JAIMC
The Journal of Allama Iqbal Medical College

January - March 2021, Volume 19, Issue 01

Editorial

Original Articles

PUBLICATION OFFICE:
Department of Psychiatry & Behavioural Sciences, Allama Iqbal Medical College / Jinnah Hospital, Allama Shabbir Amad Usmani Road Lahore (Pakistan).
Ph +92-42-99231453
Email: journal@aimc.edu.pk
drelmo@hotmail.com

JAIMC
The Journal of Allama Iqbal Medical College
January - March 2021, Volume 19, Issue 01

JAIMC
The Journal of Allama Iqbal Medical College

January - March 2021, Volume 19, Issue 01

Outstanding Reviewer of Vol.19 Issue 01 (January – March 2021)

Dr. Muhammad Qasim Muneer

Dr. Muahmmad Qasim Muneer graduated from FMH College of Medicine and Dentistry, Lahore. He completed his M.Phil in Anatomy in 2017 from Post graduate Medical Institute, Lahore. He is currently working as Assistant Professor of Anatomy at Allama Iqbal Medical College, Lahore.

Pictures on Title

The JAIMC agrees to accept manuscripts prepared in accordance with the "Uniform Requirements submitted to the Biomedical journals as approved by the International Committee of Medical Journal Editors (ICMJE) guidelines, published in the British Medical Journal.In year 2008, the committee revised and reorganized the entire document and incorporated the Separate Statements into the text.

Submission of Manuscripts:
All manuscripts submitted for publication should be sent exclusively to JAIMC, Lahore. Papers submitted for publication must not have been published or accepted for publication elsewhere. Authors can submit their articles by e-mail: aimcjaimc@gmail.comin Microsoft word. The JAIMC office reserves all rights of reproduction and republication of material that appears in JAIMC. If tables, illustrations or photographs are included which have been already published, a letter of permission for their republication must be obtained from the author as well as the editor of the journal in which it was printed previously.
All authors and co-authors must provide their contact telephone/cell numbers and e- mail addresses on the manuscript. Co-authors should not be more than six. It is mandatory to provide the institutional ethical review board/committee approval for all research articles at the time of submission of article. All submissions are subject to review /alterations by the Editor/ editorial board.

General Principles:
Authors should submit the manuscript typed in MS Word. Manuscripts should be written in English in British style/format in past tense and third person form of address. Sentence should not start with a number or figure. The manuscript should be typed in double spacing as a single column on A4, with white bond paper with one inch(2.5cm) margin on one side in Times New Romanstyle (12font). Pages should be numbered consecutively through the last page of type written material. The material submitted for publication may be in the form of an original article, a review article, a case report or letter to the editor. Original articles should report original research with about 2000 words with not more than three tables or illustrations. References should not exceed 40 in number. Short communications should be of 250 words approximately. Letter should not exceed 150 words.

Components of manuscript should be in the following sequence:

Title Page: It should include the following: article title, abstract word count, manuscript word count, and the number of tables and figures.

- **The Title of the Article**. Authors should include all information in the title that will make electronic retrieval of the article both sensitive and specific. The title should be clear and concise. The title length should not exceed more than 14 words. Do not capitalize the first letter of each word in the title unless it is a proper noun. Do not use abbreviations in the title.
- Name of authors with highest academic degrees of each, their postal addresses, fax, phone number and mobile numbers.
- The name of the department(s) and institution(s) to which the work should be attributed.
- Disclaimers, if any.
- Corresponding authors. The name, mailing address, telephone and fax numbers, and e-mail address of the author responsible for correspondence about the manuscript.

Abstract: It should be structured, not more than 250 words, briefly mentioning under following sub-headings Objectives, Design, Place and duration of study, Methods, Results and Conclusion. Abstracts should be followed by 3-5 MeSH (Medical Subject Headings) words. Use appropriate terms to increase searchability of your study.

Manuscript Format:
Introduction: Present a background for the study. Include global, regional and local reports where appropriate. Cite only strictly pertinent references. State the purpose or objective of the study without sub-headings. Explain the hypothesis and the rationale of the research. Do not include data or conclusions from the current study.

Methods: Methodology should be written including study design, ethical review statement, description of the selection of the observational or experimental subjects, study setting, study duration, sampling method, sample size calculations with references, follow-up period, inclusion and exclusion criteria, operational definitions, variables(independent and dependent), identification of the methods and apparatus (provide the manufacturer's name and address in parenthesis) and identification of all drugs and chemicals in paragraph/s form. The source of the study subjects should be included and clearly described. The inclusion and exclusion criteria need to be elaborated. Any equipment used in the study

should give the manufacturer's name and address. Procedures should be clearly described so as to facilitate others to reproduce them easily. References are necessary for to established methods, statistical methods, for already published methods not well-known, substantially modified methods with the reasons for using them, along with their limitations. All drugs and chemicals used should be stated in generic name(s), dose(s), and route(s) of administration. State the statistical software package used along with the version. Exact p-values and 95% confidence interval (CI) limits must be mentioned instead of only stating greater or less than level of significance. State the statistical software package used along with the version.

Results: Emphasize or summarize only the most important observations. Give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them giving degree of freedom, test of significance value and p-value (in brackets) if any. Do not duplicate data in graphs and tables if already mentioned in text.

Discussion: The discy or introduction should not be included in the discussion. Do not repeat in detail data or other information given in other pussion should begin with a summary of the main results. These are then discussed with results of other published studies either supporting or refuting your results. Any new findings of the research should be emphasized and the relevance should be stated. These can be used for future research or clinical practice. Details of methodologarts of the manuscript, such as in the introduction or the results section. Limitations of the study should be stated at the end of the discussion in a separate paragraph.

Conclusion: It should be provided under separate headings and highlight new aspects arising from the study. It should be in accordance with the objectives.

References: Vancouver style is essential for publication in Journal of Allama Iqbal Medical College. References should be cited in consecutive numerical order as first mentioned in the text and designated by the reference number in superscript. References appearing in a table or figure should be numbered sequentially with those in text.
The Journal follows Index Medicus style for references and abbreviated journal names according to the list of Journals indexed in Index Medicus:
http://www.ncbi.nlm.nih.gov/nlmcatalog/

Tables: Data should be placed clearly and concisely to enable the reader to comprehend easily.Do not repeat the results stated in tables in the text.Tables should be numbered consecutively and cited in the results. Arabic numerals should be used.The title should be short and explanatory and written on top of the table.The columns of the table should have a short heading.Footnotes should elaborate on the abbreviations.If any data or table has been included from a published article, the source should be cited.

Illustrations: Figures and pictures should clarify and augment the text. The selection of sharp, high-quality illustrations is of paramount importance. Figures of inferior quality will be returned to the author for correction or replacement. For x-ray films, scans, and other diagnostic images, pictures of pathology specimens or photomicrographs, high-resolution photographic image files are recommended. Legend should be placed below the figure and detailed explanations should be given as legends and not on the illustrations. Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should stand out on the background. Figures should have consecutive numbers and should be cited in the results accordingly in the text and written as “Figure”. Arabic numerals should be used. Any symbols, arrows, numbers, or letters used to identify parts of the illustration should be explained clearly in the legend. Original illustrations should be submitted; previously published illustrations are not preferred. If a figure is taken from a previous publication, the source should be given as a reference. Written permission from the publisher should be provided by the author on submission of the manuscript.

SAVIOR OF THE LEPERS

How to cite: Imran M. Saviors of the lepers. JAIMC. 2021; 19(1): iii-v

Leprosy also known as Hansen's disease is caused by *Mycobacterium leprae*. It is a chronic disease transmitted through droplets from the nose and mouth during close and frequent contact with the untreated cases, but is not highly infectious. The bacterium divides very slowly and has an incubation period of over five years.[1] The symptoms can take as long as 20 years to appear. If the disease is left untreated, leprosy can cause progressive and permanent damage to the skin, nerves, limbs and the eyes. Leprosy is treatable, and the cure provided in the early stages of the disease averts crippling lifelong disability. Early prompt diagnosis and treatment with multidrug therapy (MDT) stay the key factors in eliminating leprosy as a public health concern. WHO has made MDT available free of cost to all the patients worldwide since 1995.[1]

Previously, leprosy was feared as a highly contagious, chronic devastating illness, but now, with time and research, it is known that the bacterium is hard to spread and it is effectively curable once diagnosed. But to date, a lot of social stigma and prejudice remains about the disease, and the people suffering from the illness are discriminated and isolated in many areas where leprosy is common. Continued efforts and commitment to fighting the disease stigma through health education and improving the access to treatment will lead to a leprosy free world.[2]

Leprosy has been misunderstood and feared throughout the history. Origin of the disease is unknown, however it was first described around 600 B.C. In 1960s and 1970s, there was a debate about the choice of appropriate name for this illness; leprosy, lepra, Hansen's disease or Hanseniasis. Even a strong movement spread in some regions globally to substitute the name Hansen's disease for leprosy. Leprosy is not just is an important cause of crippling deformities, but the affected people have high psychosocial affects as well, such as divorce, unemployment, and displacement from their native place to isolations. Psychiatric disorders are frequent in such patients and these preoccupy the healthcare resources. Comorbidity among these patients is observed in epidemiological and clinical studies.[3]

January 28 is marked globally as the World Leprosy day. Leprosy is an indigenous as well as a migration problem in our country. Indigenous leprosy is found in all provinces of Pakistan, however in strictly focal pattern, places of high prevalence being interspersed with regions where the disease is unknown. Migration plays a pivotal role in the epidemiology of leprosy In Pakistan.[4] Affected people have migrated from all neighboring areas like Iran, Afghanistan, India, the latter one contributing the largest population of migrated patients in Pakistan. Each province has its own peculiar migration problems, caused by permanent as well as seasonal migrations. In 1904, the British Leprosy Mission, setup the Rawalpindi Leprosy Hospital, which is the oldest facility dedicated to the treatment of leprosy in Pakistan. Now located in a populated part of the city, at the time of its establishment, the hospital was a deserted place in the outskirts of Rawalpindi. Lepers from all over British India used to come here for shelter and treatment. Since 1968, the hospital has been run by the organization Aid to Leprosy Patients (ALP). There are currently 97 beds for leprosy patients. The hospital also runs a tuberculosis control programme and provides facilities related to skin problems, blindness, psychotherapy and rehabilitation. Every year, approximately 400 to 500 new leprosy cases are registered all over Pakistan. In 2019, 413 leprosy cases were registered, of them 71 cases were found deformed. This accounts for 17 percent of all registered patients. Sindh has the greatest number of leprosy patients from Pakistan.[4] Leprosy is a disease that is totally curable if diagnosed early. However, without an improved active case detection, early diagnosis and prompt treatment, the number of patients at risk of developing impairments and disabilities remains very high. Of every 100 people newly diagnosed with this illness in Pakistan, 15 already have impairments. Annual leprosy statistics in Pakistan show that the number of new case detections is slowly decreasing as a long-term trend, however, more efforts are needed to stop this disease.[3,4]

Leprosy used to be associated with mutilation, isolation and suffering. Even in today's world, leprosy is still considered as God's punishments in some developing countries, including Paktsian, and person who have it are considered "unclean". Even the disease is curable and drugs are available free of charge, in many developing countries, the disease is often not even diagnosed because there are not

enough treatment centers. One German doctor has worked wonders in Pakistan. Ruth Katherina Martha Pfau (9 September 1929 – 10 August 2017) was a German–Pakistani Catholic nun of the Society of the Daughters of the Heart of Mary and a physician. She moved to Pakistan from Germany in 1961 and devoted more than 55 years of her life to fighting this disease in Pakistan. Ruth Pfau was honoured with Hilal-i-Pakistan, Hilal-i-Imtiaz, Nishan-i-Quaid-i-Azam, and the Sitara-i-Quaid-i-Azam by the Government of Pakistan. She contributed to the establishment of 157 leprosy clinics across Pakistan that treated thousnads of pateints with leprosy. Fazaia Ruth Pfau Medical College and Dr. Ruth Pfau Hospital are named after her in Karachi.[5]

In 1960, at the age of 31, Pfau decided to dedicate the rest of her life to the people of Pakistan and their battle against leprosy outbreaks. She visited the Lepers' Colony behind McLeod Road (now I. I. Chundrigar Road) near the City Railway Station Here she decided that the care of lepers would be her life's calling. She started medical treatment of lepers in a hut in this area. The Marie Adelaide Leprosy Centre was founded and Dr. I K Gill started social work for the leprosy patients and their families. A leprosy clinic was bought in April 1963 and patients from different regions of Pakistan and from Afghanistan started coming for the treatment.[6]

In 1979, Pfau was appointed as the Federal Advisor on Leprosy to the Ministry of Health and Social Welfare of Government of Pakistan. Pfau travelled to far furlong areas of Pakistan where there were no medical facilities for the lepers. She collected donations in Germany and Pakistan and coordianted with hospitals in Rawalpindi and Karachi. In recognition of her service to the country, she was awarded Pakistani citizenship in 1988. In 1996 Pakistan was declared by W.H.O. as one of the first countries in Asia to have controlled leprosy because of her untiring effects. Pfau died at the Aga Khan University Hospital in Karachi on 10th August 2017. The state funeral was held at Saint Patrick's Cathedral, and she was buried at a Christian cemetery in Karachi.[7]

Ruth Pfau's services to end leprosy in Pakistan can never be forgotten. She left Germany and made Pakistan her home to serve humanity. She may have been born in Germany; her heart was always in Pakistan. She came here to make lives better for those affected by the disease and in doing so found herself a home. Pakistani nation will remember her for her courage, loyalty, her services in eradication of leprosy and most of all her patriotism. Pakistan referred to Pfau as an "ambassador of humanity".[6]

There are numerous obstacles for the complete eradication of this disease from Pakistan. Although a lot has been done and success obtained in many areas, the problem of stigma remains. Leprosy eradication is a long-term act. Drug treatment alone is not enough to solve all the management issues. The role of mental health professionals is mandatory in dealing with psychosocial problems related to leprosy. Psychosocial assistance and support to the lepers will be helpful in eradication of this disease.[8] This requires a national wide campaign of health education for the general public. The general public must be made aware that leprosy is not a genetic or hereditary disease, however it is totally curable, and the affected patients need social support. A better coordination between all healthcare workers dealing with the lepers will settle all the issues and help in achieving the eradication goals in the country.[8]

References

1. K.C., S., K.C., G., Gyawali, P. *et al.* Leprosy – eliminated and forgotten: a case report. *J Med Case Reports* 13, 276 (2019). https://doi.org/10.1186/s13256-019-2198-1
2. Herekar FF, Ashraf H, Salahuddin N. Leprosy manifesting with type 2 leprae reactions in a patient presenting with chronic fever: A case report. J Pak Med Assoc. 2018; 68:653–5. PMid:29808061
   Operational Manual Global Leprosy Strategy 2016−2020
3. World Health Organization.
4. New leprosy cases registered in Karachi. Published in The Dawn, January 28th, 2019.
   "Sister Ruth Pfau, 'Mother Teresa of Pakistan' obituary"
5. The Telegraph. 14 August 2017.
6. Aqeel, Asif (12 August 2017). "Master of her own destiny, saviour of others". Daily Times.
7. Mutaher, Zia (2004). Serving the Unserved: The Life of Dr Ruth Pfau. Karachi: City Press. ISBN 9698380728.
8. The Global Leprosy Strategy 20162020: Accelerating towards a leprosy-free world. World Health Organization

Dr. Muhammad Imran
Managing Editor JAIMC
drelmo@hotmail.com

Not all of us can prevent a war; but most of us can help ease sufferings of the body and the soul.

Dr. Ruth Pfau

CLINICAL, RADIOLOGICAL AND HISTOPATHOLOGICAL EVALUATION OF OVARIAN MASSES

Asifa Alia,[1] Maria Hussain,[2] Zunaira Bajwa,[3] Zill-e-Huma,[4] Amir Nazir[5]

How to cite: Alia A, Hussain M, Bajwa Z, Huma Z, Nazir A. Clinical, radiological and histopathological evaluation of ovarian masses. JAIMC. 2021; 19(1):1-7.

Abstract

Background: Ovarian masses are the growths outside or inside the ovaries which disturbs the menstrual cycle and fertility of the females.

Objectives: To determine the clinical, radiological and surgical evaluation of ovarian masses

Methodology: This Cross sectional study was done in the department of Obstetrics & Gynecology in Rai medical college / Doctor's Trust Teaching Hospital, Sargodha from June 2019 to June 2020. Sample size consisting of 63 patients were selected using consecutive non probability sampling method with clinical diagnosis of ovarian masses. These patients underwent transvaginal ultrasonography and findings were recorded. Blood sample was taken for tumor markers and base line investigations. Meanwhile, surgery was done including hysterectomy or bilateral salpingo-Oophorectomy surgical and histopathological evaluation of ovarian masses was done.

Results: The mean age of females was 41.76 ± 14.93 years. Age of menarche was 13.05 ± 1.05 years. Duration of abnormal symptoms was 11.38 ± 12.09 months. Abdominal pain was the most common symptom for ovarian mass [54 (85.7%)]. On clinical examination for ovarian masses, palpable mass was observed in 27 (42.9%) cases, tenderness 48 (76.2%), irregularity 36 (61.9%), cervix was normal in 45 (71.4%) cases, cervical deviation 12 (19%). On ultrasound cyst wall thickness was increased in 39(61.9%), septations 21(33.3%), internal echoes 30(47.6%), abnormal uterine size 39(61.9%) and 3 (4.8%) cases had metastasis. The most common surgical procedure performed were total abdominal hysterectomy and Bilateral Salpingectomy [33 (52.3%) each]. On chemical pathology, abnormal findings were recorded as CA125 in 10 (15.9%) cases, α-Fetoprotein level in 3 (4.7%), Beta HCG in 5 (7.9%), Carcinoembryonic antigen in 2(3.0%), Lactate dehydrogenase in 2(3.0%) cases. Histopathological findings of biopsy sample were as follicular cyst was most common [21 (33.3%)].

Conclusion: Our study showed that the chances of abnormal findings on ultrasound and surgery are high in symptomatic females with ovarian mass.

Key Words: ovarian masses, ultrasonography, CA125, biopsy, total abdominal hysterectomy, bilateral salpingo-opherectomy

The normal functioning ovary produces a follicular cyst 6-7 times each year. In most cases, these functional cysts are self-limiting and resolve within the duration of a normal menstrual cycle. In rare situations, a cyst persists longer or becomes enlar-ged. At this point, it represents a pathological adnexal mass.[1]

In the past, physicians relied on the findings of a pelvic examination to diagnose an adnexal mass. With the introduction of imaging modalities including transabdominal and vaginal ultrasonography. Doppler color scans, and magnetic resonance imaging, more characterization of the internal wall structure is possi-ble. Although not

1. Asifa Alia
2. Maria Hussain
3. Zunaira Bajwa
4. Zill-e-Huma
5. Amir Nazir

1,2,3. Rai Medical College Sargodha
4. Amna Inayat Medical College Lahore
5. Sargodha Medical College, Sargodha

Correspondence:
Dr. Asifa Alia, Assistant Professor Gynae and Obstetrics. Rai Medical College Sargodha. Email: tariqasifa14@gmail.com

Submission Date: 28-09-2020
1st Revision Date: 16-10-2020
2nd Revision Date: 25-10-2020
Acceptance Date: 30-10-2020

definitive, these findings can help determine whether a mass appears more consistent with a physiologic cyst or neoplastic process. [2]

Possible lab tests in the evaluation of adnexal mass include serum markers, Complete blood count, urinalysis and electrolytes.[1] CA-125 is elevated in approximately 80% of all women with ovarian cancer. Among gynecological cancers, ovarian malignancy is the most lethal, largely due to the fact that it is not diagnosed until late stage.[3] A female's risk at birth of having ovarian tumor sometime in her life is 6-7%. Relative frequency of ovarian tumor is different for western and Asian countries. Two third of ovarian tumors occur in women of reproductive age group.[4]

The distribution of ovarian cancer histology varies widely worldwide. Variation in the distribution of histological groups of ovarian cancer may impact international comparisons of survival from all ovarian cancers combined if countries with more favourable histological distributions, where more tumours are classified as type I epithelial, germ cell or sex cord-stromal, are compared to survival in countries with higher proportions of type II epithelial tumours.[5]

The aim of this study is to determine the clinical, radiological, surgical and histopathological evaluation of ovarian masses in symptomatic females. There was a need to update the current extent of problem and output of current practice in local population.

METHODOLOGY

Study Design: Cross sectional study.

Setting: Department of Obstetrics & Gynecology, Rai medical college / Doctor's Trust Teaching Hospital, Sargodha.

Duration: One year months i.e. June 2019 to June 2020

Sample Size: With confidence level 95%, margin of error 10% and anticipated population proportion 78.9% for benign ovarian masses then sample of 63 was calculated.

Sampling Technique: Non probability consecutive.

Selection Criteria: Females of age 20-70 years, presenting with symptoms of ovarian masses / lesion i.e. severe abdominal pain, nausea, lower backache and thighs pain, abnormal vaginal bleeding were included. While females with recurrent lesions, ovarian or endometrial malignancy or metastatic disease were excluded.

Patients presented in out patient Department of Obstetrics & Gynecology, Rai medical college / Doctor's Trust Teaching Hospital, Sargodha. Informed consent was taken before enrollment and females who fulfilled selection criteria were enrolled. Details like age, parity, symptoms, history of smo-king, alcoholism, comorbidities and medical history were also noted. Clinical examination of all patients was done and blood sample was taken for assessment of hormonal level (CA-125, Beta HCG, CEA, LDH). Then females underwent ultrasonography for assess-ment of size and location of ovarian mass and endo-metrium was also observed. Then females underwent surgery including hysterectomy either total abdominal or vaginal, bilateral salpingo-Oophorec-tomy, etc. Samples of ovarian mass were sent to the histopathology department for assessment of type of mass either malignant or benign.

Data Analysis: Data analysis done with SPSS v 20. Mean and standard deviation calculated for age & duration of symptoms etc. Frequency & Percentage calculated for symptoms, comorbidities, patient history, surgical, radiological and histopathological findings.

RESULTS

The mean age of females was 41.76 ± 14.93 years. There were 30 (47.6%) females of reproductive age group, 21 (33.3%) were in perimenopause stage while 12 (19%) had postmenopausal stage. There were only 12 (19%) nulliparous females, while 42 (66.7%) had parity <5, but 9 (14.3%) had parity >5. Age of menarche was 13.05 ± 1.05 years. Duration of abnormal symptoms was 11.38 ± 12.09

months. Abdominal pain was the most common symptom for ovarian mass [54 (85.7%)], followed by pressure symptoms [24 (38.1%)], abnormal uterine bleeding [18 (28.6%)], urinary frequency [18 (28.6%)]. Only 9 (14.3%) females had history of contraception used and all had IUCD implant. Table 1

On clinical examination for ovarian masses, palpable mass was observed in 27 (42.9%) cases, tenderness in 48 (76.2%) cases, abnormal consis-tency in 39 (61.9%) and abnormal regularity in 39 (61.9%) cases. On ultrasound, cervix was normal in 45(71.4%) cases while cervical deviation was detec-ted in 12

Table 1: *Demographics and Clinical Findings of Females with Ovarian Masses*

Parameters	Mean ± SD / f (%)
n	**63**
Age (years)	41.76 ± 14.93
Reproductive age (18-40 years)	30(47.6%)
Perimenoausal (41-55 years)	21(33.3%)
Postmenopausal (>55 years)	12 (19%)
Parity	
Nulliparous	12 (19%)
Multiparous (<5)	42(66.7%)
Grand multiparous (>5)	9 (14.3%)
Ovarian mass symptoms	
Duration of abnormal symptoms	11.38 ± 12.09
Pressure Symptoms	24(38.1%)
Urinary urgency	12 (19%)
Urinary frequency	18(28.6%)
Abdominal pain	54(86.7)
Generalized plain	27(42.9%)
Localized pain	24(38.1%)
Pain intensity	
Mild	27(42.9%)
Moderate	27(42.9%)
Severe	9 (14.3%)
Menstrual cycle	
Age of menarche	13.05 ± 1.05
Irrirr Irregular bleeding	18(28.6%)
Post-menopausal Bleeding	6(9.5%)
Premenopausal	48(76.2%)
Postmenopausal	15(23.8%)
Medical history	
Contraception (IUCD)	9 (14.3%)
Medical Treatment for ovarian masses	18(28.6%)
Surgical Treatment for ovarian masses	6(9.5%)

Table 2: *Clinical, Radiological and Surgical Evaluation of Ovarian Masses*

Parameter	F (%)	
Clinical findings		
Palpable Mass	27 (42.9%)	
Not palpable	36(57.1%)	
Abnormal Consistency	39(61.9%)	
Abnormal Mobility	48(76.2%)	
Abnormal Regularity	39(61.9%)	
Tenderness	48(76.2%)	
Cervix Normal	45(71.4%)	
Cervical Deviation	12 (19%)	
Ultrasound findings		
Site		
Right adnexa	33(52.4%)	
Left adnexa	30(47.6%)	
Increased cyst wall thickness	39(61.9%)	
Abnormal Septation	21(33.3%)	
Internal echos	30(47.6%)	
Abnormal Uterine size	39(61.9%)	
Doppler findings		
Low grade vascularity	3(4.8%)	
Minimal flow	51(81.0%)	
No flow	6(9.5%)	
Metastasis	3(4.8%)	
Surgical findings		
Fallopian Tube	R	L
Normal	30(47.6%)	36 (57.1%)
Adherent	9 (14.3%)	9 (14.3%)
Gangrenous	3(4.8%)	0(0%)
Involved in mass	12 (19%)	9 (14.3)
Stretched	3(4.8%)	6 (9.5%)
Swollen hydro-salpinx	6(9.5%)	3 (4.8%)
Metastasis observed	3(4.8%)	
Adhesions	27(42.9%)	
Procedure performed		
Total abdominal hysterectomy	33(52.3%)	
Bilateral Salpingectomy	33(52.3%)	
Cystectomy	12 (19%)	
Unilateral salpingo-oophorectomy	12 (19%)	
Diagnostic Laparotomy	6(9.5%)	
Vaginal hysterectomy	3(4.8%)	
Drainage of multiple fluid filled spaces	3(4.8%)	
Chemical Pathology		
Abnormal CA125 level	10 (15.19%)	
Abnormal α Fetoprotein level	3 (4.7%)	
Abnormal Beta HCG	5 (7.9%)	
Abnormal Carcinoembryonic antigen	2 (3%)	
Abnormal Lactate dehydrogenase	2(3%)	
Histopathological findings of biopsy sample		
Follicular cyst / Serous Cyst adenoma	21(33.3%)	
Chorionic Villi suggestive of Chronic ectopic Pregnancy	9 (14.3%)	
Dermoid cyst	9 (14.3%)	
Endometriosis	8 (12.6%)	
Hemorrhagic cyst	8 (12.6%)	

(19%) cases, abnormal cyst wall in 39 (61.9 %) cases, 21 (33.3) had abnormal septation, while all (100%) females had abnormal endometrium. On Doppler ultrasound, 3 (4.8%) cases had metastasis. On surgery, 30 right fallopian tube and 36 left fallo-pian tubes were involved. The most common surgical procedure performed were total abdominal hysterectomy and Bilateral Salpingectomy [33 (52.3%) each], followed by Cystectomy and Unilateral salpingo-oophorectomy [12 (19%) each] and diagnostic laparotomy [6 (9.5%)]. On chemical pathology, abnormal findings were recorded as CA125 in 10 (15.9%) cases, α-Fetoprotein level in 3(4.7%), Beta HCG in 5 (7.9%), Carcinoembryonic antigen in 2 (3.0%), Lactate dehydrogenase in 2(3.0%) and adhesions in 27(42.9%) cases. Histopathological findings of biopsy sample were as follicular cyst was most common [21 (33.3%)] followed by Chorionic Villi suggestive of Chronic ectopic Pregnancy and Dermoid cyst [9 (14.3%) each], Endometritis and Hemorrhagic cyst [8 (12.6%) each] and 3 (4.8%) had malignant tumors, 3 (4.8%) had leiomyoma and 2 (3%) had Mullerian duct anomly. Table 2

DISCUSSION

The largest screening trial performed to date (The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Randomized Controlled Trial, or PLCO Trial) found that among the general population, screening with CA-125 and transvaginal ultrasound versus usual care did not decrease ovarian cancer mortality. The study also reported serious complications arising from diagnostic interventions performed to evaluate false-positive screening results.[6]

While many other screening algorithms are being actively investigated, at this time there is insufficient evidence to support the routine use of pelvic ultrasound and/or CA-125 to screen for ovarian cancer in the general population. As with all screening tests, the ideal screening algorithm will ultimately balance the accurate detection of ovarian malignancy at an early stage while minimizing unnecessary interventions in patients.[6]

Most adnexal masses are benign; outcome and prognosis are very good. Generally, no impact on life span or quality of life is noted. In fact, most women treated for adnexal masses have no interruption in their reproductive abilities.[1] In our study, abdomi-nal pain was the most common symptom for ovarian mass [54 (85.7%)]. On clinical examination for ovarian masses, palpable mass was observed in 27 (42.9%) cases, tenderness 48 (76.2%), abnormal consistency 39 (61.9%) and irregularity 39 (61.9%). Cervix was normal in 45(71.4%) cases, cervical deviation 12(19%). On ultrasound abnormal cyst wall 36(61.9%), internal septation 21(33.3%), internal echoes 30(47.6%). The most common surgical procedure performed were total abdominal hysterectomy and Bilateral Salpingectomy [33(52.3%) each], adhesions in 27 (42.9%) cases. On chemical pathology, abnormal findings were recorded as CA125 in 10 (15.9%) cases, α-Fetoprotein level in 3 (4.7%), Beta HCG in 5 (7.9%), Carcinoembryonic antigen in 2 (3.0%), Lactate dehydrogenase in 2 (3.0%). Histopathological findings of biopsy sample were as follicular cyst was most common [21(33.3 %)]. Germ cell tumors were found in 2 patients and mucinous adenocarcinoma in 1 patients.

Those women who are found to have malignant adnexal masses fall into 3 groups, as follows: Women 18-20 years: Germ cell tumors are seen in these women. The tumors are generally confined to the ovary and are cured in 90% of women after chemotherapy.[1] Women aged 40-60 years: Epithelial tumors are the most common ovarian cancer in these women. These tumors are advanced (stage III-IV) in more than 50% of women. Even after the use of chemotherapy, only 10-40% of patients survive their disease.[1] Women >60 years: Ovarian epithelial malignancies are common in this group of patients. Metastatic malignancies are also common. The incidence of sex-cord stromal tumors also increases in incidence in this age group, although it still accounts for only 5% of tumors. Stromal tumors are often early stage and may have an indolent course.[1]

In a study, conducted in Peshawar, the frequen-

cy of malignant ovarian tumors was 10.29%, out of which Granulosa cell tumors were present in 28.6%, Endometriod Carcinoma in 28.6%, Mucinous Cystadeno Carcinoma in 14.3%, Dysgerminoma in 14.3%.[7] While Bukhari et al., found that the frequency of malignant ovarian tumors was 20%, out of which Granulosa cell tumors were present in 17%, Mucinous Cystadeno Carcinoma in 17%, Dysgerminoma in 2%, clear cell carcinoma in 2%, germ cell tumors in 26%.[8] Iyoke et al., reported that there were 206 gynecological cancers. There were 54 cases of primary ovarian cancer giving an incidence rate of 1/405 gynecological admissions per year or 0.3% or 2.4% per gynecological cancer per year. Epithelial ovarian cancer constituted 68% of cases of ovarian cancer.[8]

A Complete blood count helps evaluate for presence of inflammation and anemia. An infected mass such as a tubo-ovarian abscess results in an increased White blood cells count with an associated left shift. Adnexal masses rarely cause anemia, but because they often require surgical removal, this information should be known.[9-11] Urine or serum beta human chorionic gonadotropin should be obtained in women of reproductive age to rule out pregnancy and pregnancy-related etiologies of adnexal masses[9-11]

Other serum markers such as alpha-fetoprotein and lactate dehydrogenase can be helpful when a germ cell tumor is suspected. An ovarian mass in the setting of a thickened endometrial stripe or abnormal uterine bleeding, inhibin A and B may help with diagnosis of a granulosa cell tumor. Measuring other hormone levels is generally of limited value in the evaluation of adnexal masses. Obtaining estrogen and progesterone levels may be helpful in women suggested to have functional tumors, such as germ cell tumors, or if a girl younger than 12 years is being evaluated.[12]

The most commonly performed test to evaluate an adnexal mass is transabdominal or transvaginal ultrasonography.[13-15] This test helps demonstrate the presence of the mass and its location (eg, ovarian, uterine, bowel). It also provides the mass size, consistency, and internal architecture.

When an obvious epithelial ovarian malignancy is encountered, a complete staging protocol must be performed. This generally includes complete exploration of the abdomen, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymph node dissections, biopsies of the undersurface of the right and left diaphragms, and biopsies of the colic gutters followed by a maximal resection of the intra-abdominal tumor.[16] In select cases involving women with limited, early stage, low-grade ovarian cancers, a fertility sparing procedure may be considered. In some cases, resecting portions of the small bowel or colon may be necessary; therefore, preoperative bowel preparation may be warranted, as is a discussion about possible colostomy or other bowel changes.[17]

Among women undergoing laparoscopic resection of adnexal masses, a transvaginal approach for specimen removal is associated with less postoperative pain than a trans umbilical approach.[18] A female's lifetime risk of having ovarian tumor is 6.0–7.0%, and these tumors account for up to 30% of all cancers of the female genital system.[19] Surface epithelial tumors are the most common variety and accounts for approximately 65–75% of all ovarian tumors.[20] The most common type of epithelial ovarian neoplasms encountered is benign cystadenomas, of which 75% are serous cystadenomas and 25% are mucinous cystadenomas.[21] The occurrence of mixed epithelial tumors is rare, while the occurrence of two different types of ovarian tumors in each of the ovaries is very rare, with only few cases having been documented.[22]

The clinical features of ovarian cysts and tumours can vary depending on the size and type of pathology present. When taking a history from patients it is important to bear in mind that the presentation of ovarian cancer is often vague causing a delay in diagnosis and presentation to specialists with advanced disease. Therefore, never ignore a postmenopausal patient with nonspecific gynecological or gastrointestinal symptoms.[23]

CONCLUSION

Our study showed that the chances of abnormal findings on ultrasound and surgical are high in symptomatic females with ovarian mass. So in future, such cases should be screened for clinical signs & symptoms and radiological findings can also be reliable as in many cases ultrasound and surgery showed almost similar findings.

LIMITATIONS OF THE STUDY

Our study had two important limitations. Sample size was very small. Further studies are suggested to be conducted on large sample size to confirm the results as determined through this study. Moreover, there was financial problem, especially for ultrasound and blood tests. Duration of study and follow-up was very short. Further studies should be done for prolonged time and with longer follow-up duration in order to follow the prognosis of surgical procedures.

Conflict of Interest

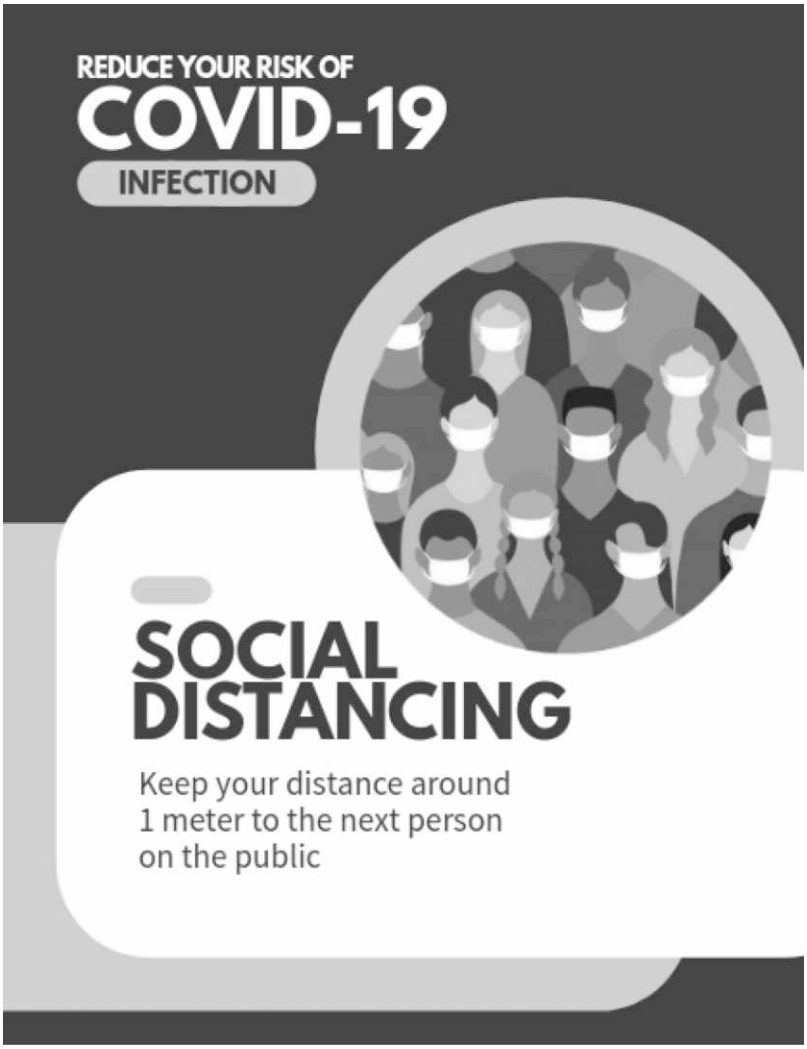
There was no conflict of interest shown by any author.

REFERENCES

1. Nelson Teng. Adnexal Tumors. 2016 [cited 2016]; Available from: http://emedicine.medscape.com/article/258044-overview#showall.
2. Sayasneh A, Ekechi C, Ferrara L, Kaijser J, Stalder C, Sur S, et al. The characteristic ultrasound features of specific types of ovarian pathology (Review). International journal of oncology 2015;46(2):445-58.
3. Onyiaorah I, Anunobi C, Banjo A, Fatima A, Nwankwo K. Histopathological patterns of ovarian tumours seen in Lagos University Teaching Hospital: a ten year retrospective study. Nig Q J Hosp Med 2010;21(2):114-8.
4. Jha R, Karki S. Histological pattern of ovarian tumors and their age distribution. Nepal Med Coll J 2008 Jun;10(2):81-5.
5. Matz M, Coleman MP, Sant M, Chirlaque MD, Visser O, Gore M, et al. The histology of ovarian cancer: worldwide distribution and implications for international survival comparisons (CONCORD-2). Gynecol Oncol 2017;144(2):405-13.
6. Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening randomized controlled trial. Jama 2011;305(22):2295-303.
7. Yasmin S, Yasmin A, Asif M. Clinicohistological pattern of ovarian tumours in Peshawar region. J Ayub Med Coll Abbottabad 2008;20(4):11-3.
8. Bukhari U, Memon Q, Memon H. Frequency and pattern of ovarian tumours. Pak J Med Sci 2011;27(4):884-6.
9. Montagnana M, Danese E, Ruzzenente O, Bresciani V, Nuzzo T, Gelati M, et al. The ROMA (Risk of Ovarian Malignancy Algorithm) for estimating the risk of epithelial ovarian cancer in women presenting with pelvic mass: is it really useful? Clinical Chemistry and Laboratory Medicine 2011;49(3): 521-5.
10. Karlsen MA, Høgdall EV, Christensen IJ, Borgfeldt C, Kalapotharakos G, Zdrazilova-Dubska L, et al. A novel diagnostic index combining HE4, CA125 and age may improve triage of women with suspected ovarian cancer—an international multicenter study in women with an ovarian mass. Gynecologic oncology 2015;138(3):640-6.
11. Miller RW, Smith A, DeSimone CP, Seamon L, Goodrich S, Podzielinski I, et al. Performance of the American College of Obstetricians and Gynecologists' ovarian tumor referral guidelines with a multivariate index assay. Obstetrics & Gynecology 2011; 117(6):1298-306.
12. Hricak H, Chen M, Coakley FV, Kinkel K, Yu KK, Sica G, et al. Complex adnexal masses: detection and characterization with MR imaging— multivariate analysis 1. Radiology 2000;214(1):39-46.
13. Castillo G, Alcázar JL, Jurado Ma. Natural history of sonographically detected simple unilocular adnexal cysts in asymptomatic postmenopausal women. Gynecologic oncology 2004;92(3):965-9.
14. Alcázar JL, Guerriero S, Mínguez JÁ, Ajossa S, Paoletti AM, Ruiz-Zambrana Á, et al. Adding Cancer Antigen 125 Screening to Gray Scale Sonography for Predicting Specific Diagnosis of Benign Adnexal Masses in Premenopausal Women Is It Worthwhile? Journal of ultrasound in medicine 2011;30(10):1381-6.
90. Twickler DM, Forte TB, Santos-Ramos R, McIntire D, Harris P, Miller DS. The Ovarian Tumor Index predicts risk for malignancy. Cancer 1999;86(11): 2280-
16. Einhorn† N, Tropé C, Ridderheim M, Boman K,

Sorbe B, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in ovarian cancer. Acta Oncologica 2003;42(5-6):562-6.

17. Schilder JM, Thompson AM, DePriest PD, Ueland FR, Cibull ML, Kryscio RJ, et al. Outcome of reproductive age women with stage IA or IC invasive epithelial ovarian cancer treated with fertility-sparing therapy. Gynecologic oncology 2002; 87(1): 1-7.
18. Ghezzi F, Cromi A, Uccella S, Bogani G, Serati M, Bolis P. Transumbilical versus transvaginal retrieval of surgical specimens at laparoscopy: a randomized trial. American journal of obstetrics and gynecology 2012;207(2):112. e1-. e6.
19. Selvaggi SM. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. 2000.
20. Scully RE. Classification of human ovarian tumors. Environmental health perspectives 1987;73:15-24.
21. Paran TS, Mortell A, Devaney D, Pinter A, Puri P. Mucinous cystadenoma of the ovary in perimenarchal girls. Pediatric surgery international 2006; 22(3): 224-7.
22. Baradwan S, Alalyani H, Baradwan A, Baradwan A, Al-Ghamdi M, Alnemari J, et al. Bilateral ovarian masses with different histopathology in each ovary. Clin Case Rep 2018;6(5):784-7.
23. TeachMe Series. Ovarian Cysts and Tumours. 2020 [cited 2020]; Available from: https:// teachme-obgyn. com/ gynaecology/ ovarian/ tumours/.



ANALYSIS OF THE RISK FACTORS OF PLACENTA PREVIA

Safia Parveen,[1] Hina Ilyas,[2] Mahpara Shaukat,[3] Zareen Amjad,[4] Rafique S,[5] Nizam Abdul Qadir[6]

How to cite: Parveen S, Ilyas H, Shaukat M, Amjad Z, Rafique S, Qadir NA. Analysis of risk factors of placenta previa. JAIMC. 2021; 19(1):8-12.

Abstract

Placenta Previa is associated with maternal morbidity and mortality. It is associated with increased risk of peripartum hysterectomy, blood transfusions and ICU admission.

Methodology: The study was conducted at DHQ Teaching hospital Sahiwal from June 2018-March 2019. A total of 50 subjects were enrolled during the study period. The mean age of the patients in the study was 30.58 + 4.63 years (Range 21 – 40 years). The average married duration was 9.66 + 4.59 years. Mean gestational age at the time of presentation to the hospital was 34.82 + 3.05.

Results: Most of the subjects were in 21 – 40 years age group. 46 (92%) of the subjects were multigravida while only 4 (8%) of the subjects were primigravida. Previous scar was present in 21 (42%) of the patients and mal-presentation of the fetus was observed in 26 (52%) of the subjects. Multigravidity and mal-presentation of the baby were significant risk factors for.

Conclusion: Placenta Previa is an obstetric emergency requiring emergency management. Feto-maternal morbidity and mortality can be reduced significantly by proper ante-natal care, timely diagnosis of placenta Previa, promoting spontaneous vaginal deliveries and effective use of family planning services. Availability of specialists and advanced level healthcare facilities can further reduce burden on healthcare services.

Key Words: Placenta Previa, risk factor, pregnancy

Placenta Previa (PP) is a low lying placenta attached to the lower segment of uterus. It is divided into 4 grades based on the location and level of encroachment on internal OS. Grade I, II, III and IV are known as minor, marginal, partial and complete placenta previa respectively. Type I and II are commonly known as minor placenta previa while type III and IV are labelled as major placenta previa.[1] Increased maternal age, infertility treat-ment and history of previous cesarean section (CS) are common risk factors associated with placenta Previa.[2] Significant association between maternal age, booking status, male gender of the baby and type of placenta Previa has also been reported.[3]

The prevalence of placenta previa is highly variable among various geographical regions. Overall prevalence of placenta previa is reported to be 5.2 per 1000 pregnancies. Highest prevalence of 12.2 per 1000 pregnancies is reported in Asian women while lowest prevalence is 2.7 per 1000 pregnancies in sub-Saharan Africa.[4] Its prevalence is reported to be 6-fold higher in women undergoing assisted reproduction compared to those with who conceive spontaneously.[5] Studies have reported 2.75% higher incidence of placenta previa in women having history of CS.[6] Previous caesarean delivery increases the incidence of placenta previa from 10/1000 deliveries with one previous CS to 28/1000 deliveries with >3 cesarean sections. Significant increase in incidence of placenta accreta, hysterectomy and maternal morbidity has also been reported with history of cesarean section.[7]

High incidence of mortality and morbidity is

1. Safia Parveen
2. Hina Ilyas
3. Mahpara Shaukat
4. Zareen Amjad
5. Rafique S
6. Nizam Abdul Qadir

1-4. Sahiwal Medical College, Sahiwal
5. Surgery Department, Allama Iqbal Medical College, Lahore
6. DHQ Teaching Hospital, Sahiwal

Correspondence:
Prof. Safia Parveen, *Professor of Obstetrics &Gynecology Sahiwal Medical College, E- mail: drsaafia@hotmail.com*

Submission Date: 07-09-2020
1st Revision Date: 21-09-2020
2nd Revision Date: 16-11-2020
Acceptance Date: 20-11-2020

reported in parturients with abnormal placentation.[8] Placenta previa is associated with poor maternal outcome e.g. abnormal lie of the fetus, increase risk of cesarean delivery and post-partum hemorrhage. More than 50% of the mother with placenta previa has Antenatal hemorrhage (APH) requiring emergency treatment. It is a common cause of maternal death in parturients with placenta previa. Incidence of APH is positively associated with PP and varies with location and type of placenta previa.[9] Studies have also reported significant association of peripartum hysterectomy, intra and post-partum bleeding, mal-presentation of the baby, maternal sepsis and post-partum hemorrhage with placenta Previa.[2] Adverse perinatal outcomes including higher mortality rates, APGAR score <7 at birth, intra-uterine growth restriction and congenital malformations have also been reported in patients with placenta previa.[2]

High rate of vaginal bleeding, recurrent abortions, adherent placenta, placental abruption, preterm deliveries and gestational diabetes have been reported in pregnancies complicated with placenta previa.[10] Type of placenta previa has significant effect on gestational age and mode of delivery, intra-operative blood loss and birth weight of the fetus.[3] Neo-nates born to these mothers have been reported to have low APAGR score, low birth weight, prematurity, congenital malformations and frequent admissions in intensive care unit.[11] Early identification of high-risk pregnancies and careful surveillance may decrease pre and post-natal complication in mothers. Rosenberg and his colleagues concluded that timely delivery in complicated pregnancies can significantly reduce maternal and fetal complications.[12] Placenta previa is an emergency obstetric condition requiring immediate interventions to prevent morbidity and mortality in parturients. The study was planned to identify risk factors and maternal and neonatal complications associated with placenta previa.

METHODOLOGY

This was a cross-sectional observational study conducted at department of Obstetrics and Gynecology, Sahiwal Medical College teaching Hospital, Sahiwal from June 2018 to March 2019. The sampling technique was non-probability consecutive sampling. All the women having singleton pregnancies with diagnosis of placenta previa on ultrasonography were included in the study. Demographic information and gynecological & obstetric history was noted. Risk factors e.g. antepartum hemorrhage, previous caesarean delivery, mal-presentation of the baby, type of placenta previa, gravidity and parity of the patients were recorded. Record of blood and fresh frozen plasma was also maintained. Other recorded variables include maternal complication e.g. post-partum hemorrhage and duration of hospital stay and fetal complications e.g. low birth weight, intra-uterine growth restriction, still birth, early neonatal death, malformations and admission in intensive care units. All the data was analyzed using SPSS version 22.

RESULTS

A total of 50 subjects were enrolled during the study period. The mean age of the patients in the study was 30.58 + 4.63 years (Range 21 – 40 years). The average married duration was 9.66 + 4.59 years. Mean gestational age at the time of presentation to the hospital was 34.82 + 3.05 weeks (Table 1).

Multiparity, mal-presentation, availability and utilization of ante-natal care and history of previous scar were commonly reported risk factors for Placneta Previa (Fig 1).

Table 1: *Basic Information of the Subjects*

Variable	Mean	S.D
Age of the Patient	30.58	4.63
Married years	9.66	4.59
Gestational Age at Presentation	34.82	3.05
Number of Blood Transfused	4.26	2.34
Number of FFP Transfused	1.20	1.74

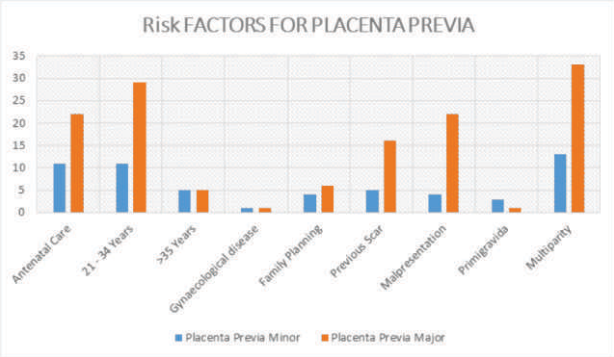


Figure 1: *Risk Factors for Placenta Previa*

Most of the subjects were in 21 – 40 years age group. 46 (92%) of the subjects were multigravida while only 4 (8%) of the subjects were primigravida. Previous scar was present in 21 (42%) of the patients and mal-presentation of the fetus was observed in 26 (52%) of the subjects. Multigravidity and mal-presentation of the baby were significant risk factors for Placenta Previa (Table 2).

Table 2: *Various Risk Factors for Placenta Previa*

Variable	Placenta Previa Minor	Placenta Previa Major	*p* - value
Maternal age in years			
21 – 34 years	11	29	0.172
≥ 35 years	5	5	
Gravidity			
Prim gravida	3	1	0.05*
Multiparity	13	33	
History of Gynecological Diseases			
Yes	1	1	0.578
No	15	33	
H/O Antenatal Visits			
Yes	11	22	0.778
No	5	12	
H/O Family Planning			
Yes	4	6	0.544
No	12	18	
H/O Previous Scar			
Yes	5	16	0.291
No	11	18	
Mal-presentation of Baby			
Yes	4	22	0.009*
No	12	12	

Only a single case of spontaneous vaginal delivery was observed. Emergency cesarean section was done in rest 49 (98%) of the patients due to complications of pregnancy, fetal distress and uncontrolled bleeding. Blood transfusion has to be done in all cases. Post-partum hemorrhage, transfusion of blood and fresh frozen plasma and duration of hospitalization were significantly greater in patients with placenta previa major compared to previa minor subjects (Table 3).

Table 3: *Maternal Outcomes in Patients with Placenta Previa*

Variable	Placenta Previa Minor	Placenta Previa Major	*p* – value
Post-partum Hemorrhage			
Yes	8	30	0.003*
No	8	4	
Ante-partum Hemorrhage			
Yes	15	32	0.959
No	1	2	
Mode of Delivery			
C-Section	16	33	0.488
Vaginal	0	1	
Blood Transfusion			
Yes	16	34	
Blood	2.94 ± 1.24	4.91 ±2.43	0.004**
FFPs	0.50 ± 1.37	1.53 ± 1.81	0.032**
Duration of Hospitalization			
< 4 days	10	3	<0.001*
> 4 days	6	31	

Table 4: *Fetal Outcomes in Patients with Placenta Previa*

Variable	Placenta Previa Minor	Placenta Previa Major	*p* - value
Still Birth			
Yes	1	4	0.544
No	15	30	
APGAR Score at 1 min			
>7	9	15	0.526
<7	6	15	
APGAR Score at 5 min			
>7	11	19	0.502
<7	4	11	
Low Birth Weight			
Yes	2	16	0.010*
No	13	14	
Early Neonatal Death			
Yes	0	1	0.475
No	15	29	
Maformations			
No	15	30	
Admission to ICU			
Yes	4	15	0.135
No	11	15	

5-cases of still birth occurred during the study which was excluded during data analysis of remaining variables. One case of early neonatal death occurred. APGAR score at 1 min and 5 min and were not significantly different in placenta previa minor and major patients. No case of malformation was seen in any of the neonate. Birth weight of the new born was significantly affected by degree of placenta Previa (Table 4).

DISCUSSION

Placenta Previa is an obstetric emergency often requiring emergency cesarean section to save mother and the fetus. Although many risk factors for Placneta Previa have been identified but little is known about its development in pregnancy. Reported risk factors for placenta Previa include history of caesarean deliveries, use of artificial reproduction techniques, infertility treatment, advanced maternal age and male gender of the baby.[3] Globally, there is an increase in rate of cesarean deliveries especially in developed countries. Moreover, rate of cesarean deliveries is almost three times greater in private sector hospitals than public sector health facilities.[13] The pooled overall prevalence of placenta Previa in China is 1.24% with significant geographical variation based on demographic characteristics of sample cohort and sampling technique.[14]

In the current study, multi-gravidity and malpresentation of the baby were significant risk factors for placenta Previa. Risk of placenta Previa is 0.63% and 0.38% in following cesarean and vaginal delivery respectively. A two fold increase in incidence of placenta Previa following first two cesarean deliveries is observed. Similarly, risk of placental abruption in subsequent pregnancies also increases.[15] Incidence of placenta Previa in subsequent pregnancies is reported to be 46% with one and 54% with two or more caesarean sections. In a study, patients with marginal placenta Previa underwent cesarean deliveries more often, delivered later and had less incidence of antepartum hemorrhage than low lying placenta.[16] Rosenberg and colleagues reported infertility treatment, advance maternal age and previous history of cesarean deliveries as independent risk factors for placenta Previa.[2]

In our study, antepartum and post-partum hemorrhage was observed in 94% and and 38% of the parturients respectively. Over results is in-line with other studies whereby researchers have reported high risk of complications with abnormally placed placenta. The pooled prevalence of antepartum hemorrhage in pregnant women is reported to be 51.6% in literature. Furthermore, the prevalence is positively correlated with multi-parity and have adverse effect on maternal outcome.[17] While pooled prevalence of post-partum hemorrhage is 22.3%. The prevalence is higher in patients with Placenta Previa compared to low lying plcaenta.[18] Antepartum and post-partum hemorrhage and adverse fetal outcome e.g. low birth weight, pre-term delivery and perinatal mortality have been associated with abnormal placentation.[19] Post-partum hemorrhage and adhesion of placenta are frequently reported following delivery in patients with central placenta.[20]

In the current study, still birth occurred in 5 (10%) of the cases. Other than low birth weight no other complications were observed in neonates owing to availability of specialized care to the patients. In a study from China, researchers reported association of low weight babies with placenta previa. However, there was no difference of APGAR score at 1min and perinatal mortality rate in both groups.[21] Anterior Placenta Previa is associated with significant increase in risk of complications in neonates.[22] In a critical analysis of outcomes of Placenta Previa, an APGAR score of <7 at 1 and 5 minutes, intra-uterine growth restriction and higher peri-natal mortality rates have been reported.[2] Much variability in associated risk factors and outcomes of placenta Previa have been reported which indicates a heterogeneous and multifactorial etiology of Placenta Previa. However, advanced maternal age and history of cesarean deliveries complicate pregnancies and should be addressed on priority basis.

CONCLUSION

Placenta Previa is an obstetric emergency requiring emergency management. Feto-maternal morbidity and mortality can be reduced significantly by proper ante-natal care, timely diagnosis of Placenta Previa, promoting spontaneous vaginal deliveries and effective use of family planning services. Availability of specialists and advanced level healthcare facilities can further reduce burden on healthcare services.

REFERENCES

1. Jauniaux E, Alfirevic Z, Bhide A, Belfort M, Burton G, Collins S, et al. Placenta Praevia and Placenta Accreta: Diagnosis and Management. BJOG: An International Journal of Obstetrics & Gynaecology. 2019;126(1):e1-e48.
2. Rosenberg T, Pariente G, Sergienko R, Wiznitzer A, Sheiner E. Critical analysis of risk factors and outcome of placenta previa. Archives of Gynecology and Obstetrics. 2011;284(1):47-51.
3. Omokanye LO, Olatinwo AWO, Salaudeen AG, Ajiboye AD, Durowade KA. A 5-year review of pattern of placenta previa in Ilorin, Nigeria. Int J Health Sci (Qassim). 2017;11(2):35-40.
4. Cresswell JA, Ronsmans C, Calvert C, Filippi V. Prevalence of placenta praevia by world region: a systematic review and meta-analysis. Trop Med Int Health. 2013;18(6):712-24.
5. Romundstad LB, Romundstad PR, Sunde A, von Düring V, Skjærven R, Vatten LJ. Increased risk of placenta previa in pregnancies following IVF/ICSI; a comparison of ART and non-ART pregnancies in the same mother. Human Reproduction. 2006; 21(9): 2353-8.
6. Marshall NE, Fu R, Guise J-M. Impact of multiple cesarean deliveries on maternal morbidity: a systematic review. American Journal of Obstetrics and Gynecology. 2011;205(3):262.e1-.e8.
7. Kavitha B, Hota B. Clinical study of placenta previa in scarred and unscarred uterus. Journal of Dr NTR University of Health Sciences. 2018;7(1):13-8.
8. Varma D, Nair A, Vindhya G, S. Management of type IV placenta previa by bilateral internaliliac artery balloon placement. Journal of Mahatma Gandhi Institute of Medical Sciences. 2015;20(2): 170-2.
9. Young BC, Nadel A, Kaimal A. Does previa location matter? Surgical morbidity associated with location of a placenta previa. J Perinatol. 2014;34(4):264-7.
10. Baumfeld Y, Herskovitz R, Niv ZB, Mastrolia SA, Weintraub AY. Placenta associated pregnancy complications in pregnancies complicated with placenta previa. Taiwanese Journal of Obstetrics and Gynecology. 2017;56(3):331-5.
11. Maiti S, Kanrar P, Karmakar C, Bagdi S. Maternal and perinatal outcome in rural indian women with placenta previa. BRITISH BIOMEDICAL BULLETIN. 2014;2(4):714 - 8.
12. Rosenberg T, Pariente G, Sergienko R, Wiznitzer A, Sheiner E. Critical analysis of risk factors and outcome of placenta previa. Arch Gynecol Obstet. 2011;284(1):47-51.
13. Singh P, Hashmi G, Swain PK. High prevalence of cesarean section births in private sector health facilities-analysis of district level household survey-4 (DLHS-4) of India. BMC Public Health. 2018; 18(1):613.
14. Fan D, Wu S, Wang W, Xin L, Tian G, Liu L, et al. Prevalence of placenta previa among deliveries in Mainland China: A PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore). 2016; 95(40):e5107.
15. Getahun D, Oyelese Y, Salihu HM, Ananth CV. Previous cesarean delivery and risks of placenta previa and placental abruption. Obstet Gynecol. 2006;107(4):771-8.
16. Ishibashi H, Miyamoto M, Soyama H, Shinmoto H, Murakami W, Nakatsuka M, et al. Marginal sinus placenta previa is a different entity in placenta previa: A retrospective study using magnetic resonance imaging. Taiwanese Journal of Obstetrics and Gynecology. 2018;57(4):532-5.
17. Fan D, Wu S, Liu L, Xia Q, Wang W, Guo X, et al. Prevalence of antepartum hemorrhage in women with placenta previa: a systematic review and meta-analysis. Scientific Reports. 2017;7:40320.
18. Fan D, Xia Q, Liu L, Wu S, Tian G, Wang W, et al. The Incidence of Postpartum Hemorrhage in Pregnant Women with Placenta Previa: A Systematic Review and Meta-Analysis. PLOS ONE. 2017; 12(1): e0170194.
19. Severi FM, Bocchi C, Vannuccini S, Petraglia F. Placenta Previa. In: Malvasi A, Tinelli A, Di Renzo GC, editors. Management and Therapy of Late Pregnancy Complications: Third Trimester and Puerperium. Cham: Springer International Publishing; 2017. p. 179-90.
20. Juntao Zheng AUSLAUJX. Prognosis and related risk factors of patients with scarred uterus complicated with central placenta previa. Prognosis and related risk factors of patients with scarred uterus complicated with central placenta previa. 2019; 90(4): 185-8--8.
21. Walfisch A, Sheiner E. Placenta previa and immediate outcome of the term offspring. Archives of Gynecology and Obstetrics. 2016;294(4):739-44.
22. Ahn KH, Lee EH, Cho GJ, Hong S-C, Oh M-J, Kim H-J. Anterior placenta previa in the mid-trimester of pregnancy as a risk factor for neonatal respiratory distress syndrome. PLOS ONE. 2018; 13(11): e0207061.

MEAN PLATELET VOLUME AS A NON-INVASIVE TOOL TO DIAGNOSE HYPERDESTRUCTIVE THROMBOCYTOPENIA

Saad Zafar,[1] Fauzia Aamer,[2] Fatima Saeed,[3] Muneeza Natiq[4]

How to cite: Zafar S, Aamer Fauzia, Saeed F, Natiq M. Mean platelet volume as a non-invasive tool to diagnose hyperdestructive thrombocytopenia. JAIMC. 2021; 19(1): 13-17.

Abstract

Background: Thrombocytopenia refers to a disorder in which there is a relative decrease of thrombocytes, commonly known as platelets present in the blood. The recent years has seen a number of studies on mean platelet volume (MPV) as a factor to discriminate the cause of thrombocytopenia.

Objective: To determine the diagnostic accuracy of raised mean platelet volume to diagnose hyper-destructive thrombocytopenia taking bone marrow biopsy as gold standard.

Methodology: This cross sectional study was conducted for 6 months. The Non probability sampling technique was used. Informed consent was taken from all the patients. Patients advised Bone marrow biopsy due to thrombocytopenia were enrolled. Complete blood count was done prior to Bone marrow biopsy. The mean MPV of 8.5 fl was taken as a cutoff value. Thrombocytopenic patients with MPV of >8.5 fl would be presumptively diagnosed as hyperdestructive thrombocytopenia. Confounding factors are not excluded in my research. Patient will be labeled as hyperdestructive thrombocytopenia on MPV and Bone Marrow Biopsy. All the collected data was entered and analyzed on SPSS version 20.

Results: The mean age of patients was 42.77±15.04 years. Male to female ratio was 0.87:1. The mean Hb was 11.05±0.62 g/dl. The sensitivity, specificity and diagnostic accuracy of MPV were 93.22%, 56.52% & 77.14% respectively taking bone marrow as gold standard.

Conclusion: MPV is a sensitive and reliable test to diagnose hyper-destructive thrombocytopenia.

Key Words: Thrombocytopenia, Mean platelet volume, Hyper-Destructive, Accuracy

Platelets are blood cells whose primary function is to stop bleeding working along with the coagula-tion factors. Platelets have no nucleus: they are frag-ments of cytoplasm which are derived from the mega-karyocytes of the bone marrow, and then enter the circulation. Platelet count is measured either manually using a hemocytometer, or by placing blood in an automated blood analyzer using electrical impedance, such as a Coulter counter. The normal range (99% of population analyzed) for platelets in healthy Cauca-sians is 150–400 × 10^9 per liter. The normal range has been confirmed to be the same in both sex and in the elderly.

Mean platelet volume (MPV) is a machine-calculated measurement of the average size of platelets found in blood and is typically included in blood tests as part of the Complete blood count. A typical range of platelet volumes is 7.5-11.5 fL (femtolitre), equivalent to spheres 2.65 to 2.9 µm in diameter.[1] In a study done by Kuratay et al; frequency of hyper-destructive thrombocytopenia was observed in 65 cases out of 107 patients i.e 60.7%.[2] When platelet concentration is below the normal range it is called thrombocytopenia and it can be due to either decreased production or increased destruction. Thrombocytopenia symptoms may include easy or excessive bleeding, petechiae, spontaneous bleeding from

1. Saad Zafar
2. Fauzia Aamer
3. Fatima Saeed
4. Muneeza Natiq

1. *Department of Pathology, Allama Iqbal Medical College Lahore*
2. *Department of Haematology, Services Institute of Medical Sciences, Lahore*
3. *Department of Pathology, Al-Aleem Medical College/Gulab Devi Hospital Lahore*
4. *Department of Pathology Allama Iqbal Medical College. PGMI/AMC/LGH, Lahore*

Correspondence:
Dr. Saad Zafar, *Demonstrator, Department of Pathology, Allama Iqbal Medical College Lahore. E-mail: saadzafar22@hotmail.com*

Submission Date: 02-10-2020
1st Revision Date: 18-11-2020

gums or nose, blood in urine or stools, heavy menstrual flow etc.

Inherited hemostatic disorders are relatively rare. The prevalence of von Willebrand disease has been estimated at 1 case per 1000-5000 population.[3] In contrast, acquired hemostatic disorders are common, and ITP is one of the most common autoimmune disorders. The acute self-limiting form of ITP, which is observed almost exclusively in children, occurs at a rate of 5 cases per 100,000 population, and the chronic form, which is observed mostly in adults occurs at a rate of 3-5 cases per 100,000 population.[3]

Unlike hemophilia, most inherited disorders of platelets are not X-linked, and they are equally distributed in both sexes. Acute ITP is also observed equally in both sexes. Chronic autoimmune thrombocytopenia is more common in females than in males.[3]

The thrombocytopenia can be either due to increased destruction in the vessels and is called as hyperdestructive thrombocytopenia e.g. in immune thrombocytopenic purpura (ITP) and other autoimmune states (SLE, CLL, lymphoma) & Infection (HIV, dengue, malaria). On the other hand it can be due to decreased production from bone marrow called hypoproductive thrombocytopenia e.g seen in Marrow failure in aplastic anaemia, Marrow infiltration by leukaemia, myelofibrosis, lymphoma, metastatic carcinoma, Marrow suppression by cytotoxic drugs and radiotherapy & viral infections (e.g. HIV, parvovirus).[4]

Bone marrow biopsy is the ultimate gold standard test to check for adequacy of megakaryocytes in bone marrow.[5] Adequate megakaryocytes indicates peripheral destruction of platelets and decreased megakaryocytes show hypoproductive thrombocytopenia. Bone marrow biopsy is an invasive test and carries its own morbidity.[6] Patients are often reluctant to undergo this test despite counseling and adequate analgesia due to pain associated with procedure and post-operative pain.[7]

On peripheral smears it is often seen that size of platelets is large in diseases associated with peripheral destruction of platelets and small sized platelets are seen in diseases where there is decreased production of platelets from bone marrow. This observation strongly reflects the importance of Mean Platelet Volume which can be used as a less invasive parameter to predict the type of thrombocytopenia.[8]

In a study conducted at Department of Haematology, Addenbrooke's NHS Trust, Cambridge, UK, where 473 unselected patients with thrombocytopenia were studied. The mean platelet volume (MPV) was 8.1 fl in patients with marrow disease and 9.8 fl in patients without marrow disease which suggests that MPV can strongly guide the clinician for the presence or absence of bone marrow disease in thrombocytopenic patients.[9] Another international study was conducted in Thailand by Numbenjapon et al completely evaluated. One hundred two patients and concluded that when compared with the BM examination, the MPV could predict hyperdestructive thrombocytopenia with a sensitivity of 82.3% a specificity of 92.5%.[10]

Rationale of this study is to determine the diagnostic significance of MPV in determining hyperdestructivethrombocytopenias. No local study has been conducted in the city so far. This may guide our clinician/physician for subsequent management and improving quality of life of the patient. The objective of the study was to determine the diagnostic accuracy of raised mean platelet volume to diagnose hyperdestructive thrombocytopenia taking bone marrow biopsy as gold standard.

METHODOLOGY

Study Design: Cross sectional study

Setting: Hematology Section, Pathology Department AIMC/JHL

Duration: 6 months i.e. 6-9-2016 to 6-3-2017

Sample Size: Sample size of 105 cases was calculated with 95% confidence level and 8% margin of error for sensitivity, 82.3% and 7% margin of error

for specificity, 92.5% and taking expected percentage of hyper-destructive thrombocytopenia i.e. 60.7%2of raised mean platelet volume MPV by taking Bone Marrow Biopsy as gold standard

Sample Technique: Non probability sampling technique (consecutive type)

Sample Selection

Inclusion Criteria: Patients of age between 18 to 70 years of either gender, presenting with thrombocytopenia diagnosed during last 1 month were included. It was defined as platelet count below 150,000/µl measured by Sysmex KX 21 and verified by manually counting on peripheral smear under microscope.

Exclusion Criteria: Patients on treatment for thrombocytopenia e.g. Steroids, IV immunoglobulins, inj Anti-D or with history of recent platelet transfusion were excluded.

Data Collection: Cases which fulfill the selection criteria were enrolled in my study from OPD and inpatient departments. Informed consent was obtained from every patient. Demographic information like age, sex, contact number and address can be obtained. All information acquired through prepared Questionnaire/Performa.Patients advised Bone marrow biopsy due to thrombocytopenia was enrolled. Complete blood count was done prior to Bone marrow biopsy. The mean MPV of 8.5 fl was taken as a cutoff value. Thrombocytopenic patients with MPV of >8.5 fl would be presumptively diagnosed as hyperdestructive thrombocytopenia. Confounding factors are not excluded in my research. Patient will be labeled as hyperdestructive thrombocytopenia on MPV and Bone Marrow Biopsy. Hyperdestructive thrombocytopenia was defined as increased peripheral destruction of platelets in circulation resulting in low platelet count less than 150,000/ul with adequate megakaryocytes in bone marrow shown on Bone marrow biopsy. On MPV it will be labeled if MPV >8.5fl.

Data Analysis: The data was entered and analysed through SPSS version 20. 2×2 table was generated to calculate the specificity, sensitivity, positive predictive value, negative predictive value and diagnostic accuracy of MPV by taking Bone Marrow Biopsy as gold standard.

RESULTS

The mean age of the patients was 42.77±15.04 years. In this study 49(46.67%) patients were male and 56(53.33%) patients were females. The mean Hb was 11.05±0.62 g/dl, mean WBC was 7.2±1.7×10^9/L, mean platelet count was 82±31×10^9/L, mean MPV was 9.30±1.16fl and mean megakaryocytes were 1.87±1.18. Table 1

The sensitivity, specificity, PPV, NPV and diagnostic accuracy of MPV was 93.22%, 56.52%, 73.33%, 86.67% and 77.14% respectively taking bone marrow as gold standard. Table 2

Sensitivity: 93.22%, Specificity: 56.52%, PPV: 73.33%, NPV: 86.67%, Diagnostic Accuracy: 77.14%

DISCUSSION

Thrombocytopenia can be due to hyperdestruction of platelets, hypo-production of platelets or abnormal spleenic pooling. Many a clinician would agree that thrombocytopenia is one of the most critical and difficult clinical conditions to manage. Hence the need for a platelet count has increased

Table 1: Baseline Characteristics of Patients

n	105
Age (years)	42.77±15.04
Male	49 (46.7%)
Female	56 (53.3%)
Hb (g/dl)	11.05±0.62
WBC	7.2±1.7×10^9/L
Platelets	82±31×10^9/L
MPV	9.30±1.16
Megakaryocytes	1.87±1.18

Table 2: Baseline Characteristics of Patients

		Bone marrow		Total
		Positive	Negative	
MPV	**Positive**	55	20	**75**
	Negative	4	26	**30**
Total		**59**	**46**	**105**

over the years in most clinical laboratories. However, the information available on platelets is not restricted to the counts alone. MPV has been evaluated as a diagnostic tool in different conditions with thrombocytopenia with variable results.[11-13]

According to our study results the MPV diagnosed positive(>8.5 fl) thrombocytopenia in 75(71.43 %) patients and it diagnosed negative(8.5fl or less) thrombocytopenia in 30(28.57%) patients. In our study the sensitivity, specificity, PPV, NPV and diagnostic accuracy of MPV was 93.22%, 56.52%, 73.33%, 86.67% and 77.14% respectively taking bone marrow biopsy as gold standard. In a study done by Kuratay et al; frequency of hyperdestructive thrombocytopenia was observed in 65 cases out of 107 patients i.e 60.7%.[2]

A study by Pritam Sewakdas Khairkar et al[14] described that the MPV is a sensitive and reliable indicator for diagnosis of thrombocytopenia due to various causes. More attention should be paid to MPV along with other platelet indices to differentiate between hyperdestructive thrombocytopenia from hypoproductive and abnormal pooling thrombocytopenia as MPV is increased in hyperdestructive thrombocytopenia.[15,16]

An international study was conducted in Thailand by Numbenjapon et al completely evaluated One hundred two patients and concluded that when compared with the BM examination, the MPV could predict hyperdestructive thrombocytopenia with a sensitivity of 82.3% a specificity of 92.5%.[10]

Many studies on these parameters have shown that they can be used to determine the cause of thrombocytopenia and they have sufficient sensitivity and specificity in the diagnosis of thrombocytopenia.[17-19] In a study conducted at Department of Haematology, Addenbrooke's NHS Trust, Cambridge, UK, where 473 unselected patients with thrombocytopenia were studied. The MPV was 8.1 fl in patients with marrow disease and 9.8 fl in patients without marrow disease which suggests that MPV can strongly guide the clinician for the presence or absence of bone marrow disease in thrombocytopenic patients.[9]

One study by NH Aponte-Barrios et al[20] concluded that the Platelet-derived indices could be useful in the initial approach for the differential diagnosis of pediatric patients with thrombocytopenia. The area under the ROC curve for platelet-derived indices showed that they were adequate for defining the causes of thrombocytopenia. MPV and platelet-large cell ratio had an area under the curve of 0.89 and 0.88, respectively, while platelet size deviation width had an area under the curve of 0.903.

Another study by Lee WS and Kim T-Y21 found diagnostic performances close to 100%, with a lower performance for the platelet-large cell ratio compared to platelet distribution width and MPV, in patients with aplastic anemia and ITP. However, all of these studies were performed on the adult population. The MPV has been demonstrated to be sensitive and specific in discriminating between thrombocytopenia caused by idiopathic thrombocytopenia purpura (ITP) and by aplastic anemia.[17]

On the other hand a study by Ruchee Khanna et al showed that the MPV may provide a small initial insight into the aetiology of thrombocytopenia, it is limited by insufficient sensitivity and specificity. A bone marrow examination continues to be the gold standard to differentiate the hypoproductive and hyperdestructive thrombocytopenia.[22] Xu RL et al[23] also mentions that MPV have low sensitivity and specificity to predict the presence of bone marrow diseases in thrombocytopenic patients. It has been reported that although MPV may be used as an initial suggestion of bone marrow disease in thrombocytopenic patients, it has limited sensitivity and specificity.[24]

CONCLUSION

It has been highly suggestive in our study that the MPV is highly sensitive, specific and reliable parameter to diagnose hyper-destructive thrombocytopenia taking bone marrow biopsy as gold standard.

REFERENCES

1. Bain BJ, Lewis SM, Bates I. Basic haematological

techniques. Dacie and Lewis practical haematology 2006;4:19-46.
2. Kurata Y, Hayashi S, Kiyoi T, Kosugi S, Kashiwagi H, Honda S, et al. Diagnostic value of tests for reticulated platelets, plasma glycocalicin, and thrombopoietin levels for discriminating between hyperdestructive and hypoplastic thrombocytopenia. American journal of clinical pathology 2001; 115(5):656-64.
3. Perumal Thiagarajan. Platelet Disorders Overview of Platelet Disorders. 2016 [cited 2017]; Available from: http://emedicine.medscape.com/article/201722-overview.
4. Provan D, Singer CR, Baglin T, Dokal I. Oxford handbook of clinical haematology: Oxford University Press; 2009.
5. Bashawri LA. Bone marrow examination. Indications and diagnostic value. Saudi medical journal 2002;23(2):191-6.
6. Bain B. Bone marrow biopsy morbidity: review of 2003. Journal of clinical pathology 2005;58(4):406-8.
7. Hjortholm N, Jaddini E, Hałaburda K, Snarski E. Strategies of pain reduction during the bone marrow biopsy. Annals of hematology 2013;92(2):145-9.
8. Watson SP, Morgan NV, Harrison P. The vascular function of platelets. Postgraduate Haematology, Seventh Edition 2005:699-714.
9. Bowles K, Cooke L, Richards E, Baglin T. Platelet size has diagnostic predictive value in patients with thrombocytopenia. Clinical & Laboratory Haematology 2005;27(6):370-3.
10. Numbenjapon T, Mahapo N, Pornvipavee R, Sriswasdi C, Mongkonsritragoon W, Leelasiri A, et al. A prospective evaluation of normal mean platelet volume in discriminating hyperdestructive thrombocytopenia from hypoproductive thrombocytopenia. International journal of laboratory hematology 2008;30(5):408-14.
11. Giles C. The platelet count and mean platelet volume. British journal of haematology 1981; 48(1): 31-7.
12. Reardon D, Hutchinson D, Preston F, Trowbridge E. The routine measurement of platelet volume: a comparison of aperture-impedance and flow cytometric systems. International journal of laboratory hematology 1985;7(3):251-7.
13. Trowbridge E, Reardon D, Hutchinson D, Pickering C. The routine measurement of platelet volume: a comparison of light-scattering and aperture-impedance technologies. Clinical Physics and Physiological Measurement 1985;6(3):221.
14. Khairkar PS, More S, Pandey A, Pandey M. Role of mean platelet volume (MPV) in diagnosing categories of thrombocytopenia. Indian Journal of Pathology and Oncology 2016;3(4):606-10.
15. Wintrobe MM, Greer JP. Wintrobe's clinical hematology: Lippincott Williams & Wilkins; 2009.
16. Elsewefy D, Farweez B, Ibrahim R. Platelet indices: consideration in thrombocytopenia. The Egyptian Journal of Haematology 2014;39(3):134.
17. Kaito K, Otsubo H, Usui N, Yoshida M, Tanno J, Kurihara E, et al. Platelet size deviation width, platelet large cell ratio, and mean platelet volume have sufficient sensitivity and specificity in the diagnosis of immune thrombocytopenia. British journal of haematology 2005;128(5):698-702.
18. Reddy RS, Phansalkar MD, Ramalakshmi P. Mean Platelet Volume (MPV) in Thrombocytopenia. Blood transfusion 2014;12:2.
19. Ntaios G, Papadopoulos A, Chatzinikolaou A, Saouli Z, Karalazou P, Kaiafa G, et al. Increased values of mean platelet volume and platelet size deviation width may provide a safe positive diagnosis of idiopathic thrombocytopenic purpura. Acta haematologica 2008;119(3):173-7.
20. Aponte-Barrios NH, Linares-Ballesteros A, Sarmiento-Urbina IC, Uribe-Botero GI. Evaluation of the diagnostic performance of platelet-derived indices for the differential diagnosis of thrombocytopenia in pediatrics. Revista de la Facultad de Medicina 2014;62(4):547-52.
21. Lee WS, Kim T-Y. Mean platelet volume and platelet distribution width are useful in the differential diagnosis of aplastic anemia and idiopathic thrombocytopenic purpura. Clinical chemistry and laboratory medicine 2010;48(11):1675-6.
22. Khanna R, Nayak D, Manohar C, Dhar M. A retrospective evaluation of mean platelet volume as a discriminating factor in thrombocytopenia of hypoproductive and hyperdestructive aetiologies. Journal of Evolution of Medical and Dental Sciences 2013;2(47):9059-66.
23. Xu R-L, Zheng Z-J, Ma Y-J, Hu Y-P, Zhuang S-H. Platelet volume indices have low diagnostic efficiency for predicting bone marrow failure in thrombocytopenic patients. Experimental and therapeutic medicine 2013;5(1):209-14.
24. Chandra H, Chandra S, Rawat A, Verma S. Role of mean platelet volume as discriminating guide for bone marrow disease in patients with thrombocytopenia. International journal of laboratory hematology 2010;32(5):498-505.

A COMPARISON OF ORAL NIFEDIPINE AND TRANSDERMAL NITROGLYCERINE PATCH FOR MANAGEMENT OF PRETERM LABOUR

Farah Siddique,[1] Tayyaba Rashid,[2] Sumaira Riaz[3]

How to cite: Siddique F, Rashid T, Riaz S. A comparison of oral nifedipine and transdermal nitroglycerine patch for management of preterm labour. JAIMC. 2021; 19(1): 18-23.

Abstract

Background: Preterm birth, defined as any birth before the gestational age of 37 weeks, is responsible for most of the neonatal morbidity and mortality. In Pakistan, neonatal mortality rate is 46/1000 live births. The leading causeof neonatal death is prematurity(39.3%). Numerouspharmacological agents have been utilized to inhibit preterm labour but none has proven to be ideal. The objective of this study is to compare the efficacy of oral nifedipine and transdermal nitroglycerine in inhibiting uterine contractions for prolongation of pregnancy in preterm labour.

Methodology: Randomized clinical trial was conducted inDepartment of Obstetrics and Gynaecology Unit-II, Jinnah Hospital, Lahore in twelve months period from 01-05-2018 to 30-04-2019

Results: Age distribution of the patients shows majority of the patients i.e. 41%(n=41) in Group-A and 38%(n=38) in Group-B were between 26-30 years, mean and S.D was recorded as 28.35+3.21 in Group-A and 27.72+3.48 in Group-B, 43%(n=43) in Group-A and 37%(n=37) in Group-B with para 1-2, 34%(n=34) in Group-A and 29%(n=29) in Group-B with primi para while 23%(n=23) in Group-A and 34%(n=34) in Group-B with para 3-4, comparison of prolongation of pregnancy was done and chi square test was also applied, prolongation was achieved in 64%(n=64) in Group-A and only 33(n=33) in Group-B.

Conclusion: Comparison of efficacy of Nifedipine and Nitroglycerine in inhibiting uterine contractions for prolongation of pregnancy in preterm labour, Nifedipine is found to be more effective than Nitroglycerine

Key Words: Preterm labour, prolongation of pregnancy, efficacy,nifedipine, nitroglycerine

Preterm birth is defined by World Health Organization (WHO)[1] as any birth before 37 completed weeks of gestation, or fewer than 259 days since the first day of the woman's last menstrual period (LMP). This is further subdivided on the basis of gestational age (GA):

- extremely preterm (<28 weeks);
- very preterm (28–<32 weeks);
- moderate or late preterm (32–<37 completed weeks of gestation)

1. Farah Siddique 2. Tayyaba Rashid
3. Sumaira Riaz
1-3: *Gynae Unit II Jinnah Hospital Lahore*

Correspondence:
Dr. Farah Siddique, *Gynae Unit II Jinnah Hospital Lahore*
EmaiL: *drfarahali15@gmail.com*

Submission Date: 15-10-2020
1st Revision Date: 21-11-2020
Acceptance Date: 30-11-2020

Preterm birth rate ranges from5-18% of live births across 184 countries. This accounts for 70% of neonatal deaths and 30% of infantile deaths.[2]

In Pakistan, neonatal mortality rate is 46/1000 live births.[3] The main causes of neonatal death were prematurity(39.3%), birth asphyxia and trauma (20.9%) and sepsis (17.2%) Early detection and effective management are important steps for preventing preterm labour.

Preterm birth can be either spontaneous or iatrogenic. Spontaneous preterm birth is associated with either preterm labor (PTL) or preterm premature rupture of fetal membranes (PPROM).[4]

The main aim of treatment is not only to inhibit the uterine contractions so that patients can be transferred to the tertiary care center for best intensive neonatal care unit but also to prolong pregnancy for at least 48 hours and more so that corticosteroid

may be given for fetal lung maturity. For preterm labour the drugs given are tocolyticsand corticosteroids.[5]

Tocolytic agents available are beta mimetic, calcium channel blockers, prostaglandin synthatase inhibitors, magnesium sulphate, oxytocin receptor antagonist and uterine myometrial relaxant, nitric oxide donor nitroglycerine.[6]

Nifedipine is a type 2 calcium channel blocker which inhibits inward calcium flow through cell membranes. In Vitro it inhibits myometrial contractions, by reducing basal tone and the amplitude and frequency of contractions.[7]

Nifedipine can be administered orally or in sublingual form.The sublingual form is not recommended for treatment of preterm labor because it acts more rapidly than the oral form and can cause acute hypotension.

Contraindications to the use of nifedipine, or any of the calcium channel blockers, include hypotension, congestive heart failure, and aortic stenosis. Common side effects are flushing, headache and vertigo. Compared with placebo, nifedipine is associated with significant reduction in number of deliveries within 48 hours.[8]

When compared with beta agonists, nifedipine also lowers the risk of RDS, necrotizing enterocolitis, intra ventricular haemorrhage, neonatal jaundice and NICU admission.[9]

Nitroglycerine causes the release of Nitric oxide (NO).Nitric oxide (NO) lowers intracellular ionized calcium and causes relaxation of smooth muscle by increasing cyclic Guanine Monophosphate (cGMP). Thus NO releasing agents are reported to be effective and safe for treatment of preterm labour.[10]

Smith et al conducted a randomized, double blind placebo-controlled study with an aim to assess the efficacy of NTG as a tocolytic agent as compared to a placebo.[11] They found that transdermal nitroglycerine may reduce neonatal morbidity and mortality by decreasing the rate of preterm delivery before 28 weeks, from 20.3 to 10.8%.

Transdermal Nitroglycerine may be safe, effective, well tolerated, cost effective and non invasive method of tocolysis.[12]

Since, there is a range of options of tocolytic agents, this study aimed to find the most suitable drug with regard to its efficacy and safety.

The objective of this study was to compare the efficacy of oral Nifedipine and transdermal Nitroglycerine in inhibiting uterine contractions for prolongation of pregnancy in preterm labour

A pregnant women having regular uterine contractions (at-least one in every ten minutes) resulting in cervical changes with an estimated length of less than 01 cm or cervical dilatation of more than 02 cm after 28 and prior to 37 completed weeks of gestation.

The drug is said to be effective if it prolongs the pregnancy from 48 hours to one week

METHODOLOGY

Study Design: Randomized clinical trial

Duration of Study: Twelve months

Sample Size: Total 200 patients with 95% confidence level, 5% margin of error and taking magnitude (%) of effectiveness of Nifedipine and Nitrogly-cerine i.e. 6% and 12% respectively. These patients will be divided in two groups “A” & “B” each containing 100 patients. Group “A” will receive Nifedipineand Group “B” will receive Nitroglycerine

Sampling Technique: Non-probability: Purposive sampling technique

Settings: Department of Obstetrics and Gynaecology Unit-II, Jinnah Hospital, Lahore

Sample Selection:

Inclusion Criteria

- Age 20-35 years
- Parity: Primi gravida to Gravida 4
- Gestational age 28 to 36 weeks (by LMP)
- Single normal fetus with cephalic presentation (on USG)

- Palpable uterine contractions (3 in 10 minutes)
- Patients with cervical length of less than 1 cm or cervical dilatation more than 2cm

Exclusion Criteria

- Patients already taking other means of tocolytics i.e. MgSO4, salbutamol and indomethacin etc.
- Any fetal or maternal condition in which tocolytics are contraindicated (e.g. chorioamnionitis, pre-eclampsia, cardiac disease, diabetes mellitus, intrauterine growth restriction, fetal distress and antepartum haemorrhage) assessed on clinical examination, BSR, B.P monitoring and previous investigations. Fetal distress was recorded on CTG.
- If patient is more than 4cm dilated

Data Collection

Two hundred patients fulfilling the inclusion criteria recruited from Emergency & Out Patients' Department of Jinnah Hospital, Lahore from 01-05-2018 to 30-04-2019 were included. Subjects were randomly allocated by using random number table in two groups, each consisting of 100 patients. Group "A" was allotted to the patients administered with Nifedipine and Group "B" was allotted for patient receiving Nitroglycerine. An informed consent was obtained form the patients by informing benefits and complications of the drugs. In Group-A, Nifedipine was given 20mg oral as loading dose. If uterine contraction persisted after 1hour, additional dose of 10mg was given. If labour suppressed then maintenance dose of 10mg 6 hourly was given for 48 hours. In Group-B,Nitroglycerine 10mg transdermal patch was applied on abdomen. If contractions persisted after 1 hour, additional 10mg patch was applied (total dose 20mg). At the end of 24 hours, new 10mg patch was applied for next 24hoursBlood pressure, pulse rate and uterine contractions were recorded hourly for first 12 hours and then 4 hourly till 48 hours. The demographic information was recorded (name, age, parity, gestational age). All the information was collected through a specially designed proforma.

Data Analysis

- The collected data was analyzed accordingly by using SPSS version 20. The variables to be analyzed were including demographics (age, parity, duration of gestation etc.); and prolongation of pregnancy. Demographic variables like age and gestational age was presented as mean+SD. Outcome variable i.e. prolongation of pregnancy being a qualitative observation was also presented as frequency & percentage and chi square test was used to assess any difference between the two groups. P≤ 0.05 was considered as significant.

RESULTS

A total of 200 patients fulfilling inclusion/ exclusion criteria were enrolled to compare the efficacy of Nifedipine and Nitroglycerine in inhibiting uterine contractions for prolongation of pregnancy in preterm labour.

Age distribution of the patients show 37%(n= 37) between 20-25 years in Group-A and 31%(n=31) in Group-B, 41%(n=41) in Group-A and 38%(n=38) in Group-B were between 26-30 years while 22% (n=22) in Group-A and 31%(n=31) in Group-B were found between 31-35 yeas of age, mean and S.D was recorded as 28.35+3.21 in Group-A and 27.72+3.48 in Group-B. (Table No. 1)

Gestational age in both groups was calculated and presented in table No. 2, which shows 28-32 weeks in 43%(n=43) in Group-A and 38%(n=38) in Group-B while 57%(n=57) in Group-A and 62% (n=62) in Group-B were recorded between 33-36 weeks of gestation.

Parity of the subjects show most of the patients i.e. 43% (n=43) in Group-A and 37%(n=37) in Group-B with para 1-2, 34%(n=34) in Group-A and 29%(n=29) in Group-B with primi para while 23% (n=23) in Group-A and 34%(n=34) in Group-B with para 3-4. (Table No. 3)

Comparison of prolongation of pregnancy was done and chi square test was also applied, prolonga-

tion according to operational definition was achieved in 64%(n=64) in Group-A and 33%(n=33) in Group-B, while the p value was calculated as 0.017 which is significant. (Table No. 4)

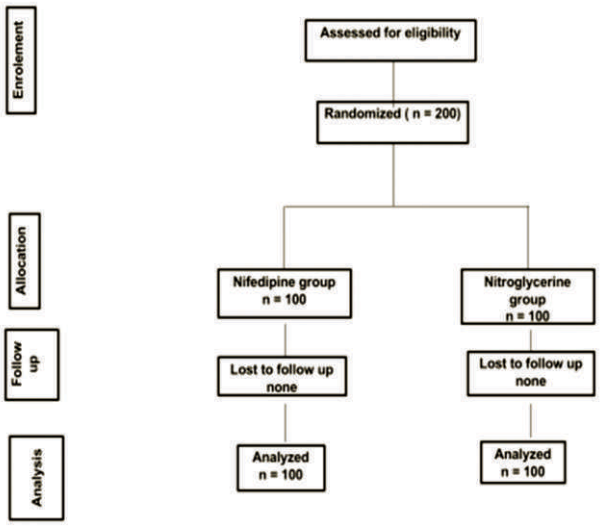


Figure 1: *Flow Chart of Different Phases of Trial*

DISCUSSION

To mitigate both maternal and neonatal risks resulting from preterm birth, current practice is to delay delivery for as long as possible. In extremely low birth weight infants, a delay of 1 week decreases neonatal mortality by 30% and allows opportunity to transfer the mother to a tertiary care facility with a neonatal intensive care unit and to administer antenatal corticosteroids. Preterm birth causes significant financial burden on the healthcare and families. The costs increase exponentially with decreasing gestational age and weight.[13]

In this study, majority of the patients i.e. (41%) and (38%) were between 26-30 years of age, mean age was 28.35+3.21 and 27.72+3.48 in Group-A and B respectively.

We recorded prolongation of pregnancy in 64% of women formore than 48 hours with nifedipine and only 33% with nitroglycerine administered group, which is showing statistically significant efficacy with nifedipine group.

Amorim et al[14] showed that the rate of preterm delivery within 48 hours after start of tocolysis was 15.4% in tocolysis with NTG and 12.5% in the nifedipine group. In the present study, nifedipine was significantly better in pregnancy prolongation beyond 48 hours (88.4 % women in nifedipine group versus 68.3% in the NTG group).

Dhawle A et al[15] compared the tocolytic effect of nifedipine and NTG in 43 and 41 patients in each group, respectively. They found that delivery within 48 hours, was significantly more with NTG as compared to Nifedipine (p=0.02). The neonatal outcomes in terms of the mean birth weight, need and

Table 1: *Age Distribution of the Patients (n=200)*

Age (in years)	Group-A (n=100)		Group-B (n=100)	
	No. of patients	%age	No. of patients	%age
20-25	37	37	31	31
26-30	41	41	38	38
31-35	22	22	31	31
Mean and S.D	**28.35±3.21**		**27.72±3.48**	
Total	**100**	**100**	**100**	**100**

Table 2: *Gestational Age of the Patients (n=200)*

Gestational age (in weeks)	Group-A (n=100)		Group-B (n=100)	
	No. of patients	%age	No. of patients	%age
28-32	43	43	38	38
33-36	57	57	62	62
Total	**100**	**100**	**100**	**100**

Table 3: *Parity Distribution of the Patients (n=200)*

Parity	Group-A (n=100)		Group-B (n=100)	
	No. of patients	%age	No. of patients	%age
Primi para	34	34	29	29
1-2	43	43	37	37
3-4	23	23	34	34
Total	**100**	**100**	**100**	**100**

Table 4: *Comparison of Prolongation of Pregnancy (n=200)*

Prolongation	Group-A (n=100)		Group-B (n=100)	
	No. of patients	%age	No. of patients	%age
Yes	64	64	33	33
No	36	36	67	67
Total	**100**	**100**	**100**	**100**

P Value= 0.017(<0.05)

duration of neonatal intensive care was similar in both groups.

Kashanian et al[16] did a randomised clinical trial comparing NTG and nifedipine as a tocolytic agent. They found that more number of women in NTG group delivered after 48 hours (52 women (86.7%) vs 41(68.3%), P=0.016) and after 7 days (47 (78.3%) vs 37 (61.7%), P=0.046), than women in the nifedipine group. Fetal outcomes like Apgar score, neonatal weight were better in NTG group. Also, the neonatal intensive care unit (NICU) admission and duration of NICU stay were less in the NTG group. Adverse effects were similar and minimal in both groups.

Nidhi Sharma et all[17] conducted a study and found transdermal nitroglycerine to be noninferior to oral nifedipine for tocolysis in preterm labor.

A local study in Pakistan Nazish Ishaq[18] et all suggested that the Nifedipine asa better tocolytic agent with good maternal and fetal safety profile as compared to another drug like Glyceryl Trinitrate.

Agustin Conde Agudelo[19] et all conducted a systematic review and meta analysis of twenty-six trials involving 2179 women. It was found that nifedipine was associated with a significant reduction in the risk of delivery within 7 days of initiation of treatment. So nifedipine should be considered as the first-line tocolytic agent for the management of preterm labor.

Agustin Conde Agudelo[20] et all conducted another systematc review and meta analysis on Transdermal nitoglycerin for the treatment of Preterm labor which includes[13] studies involving 1302 women. It was concluded that transdermal nitroglycerin was more effective than β 2-adrenergic-receptor agonists but the evidence did not support its routine use as tocolytic agent for the treatment of preterm labor.

Nice guideine[21] suggested the use of Nifedipine as first line tocolytic agent, if it is contraindicated then another agent can be used.

The results of the current study in support with other national and international studies clearly reveal that nifedipine is more effective than nitroglycerin for prolongation of pregnancy in preterm labour.

The strength of the study was that it was randomised controlled trial with adequate sample size. The limitation of the study was that it did not include comparison of any side effects of both drugs, for which any further trial may be conducted at local level.

CONCLUSION

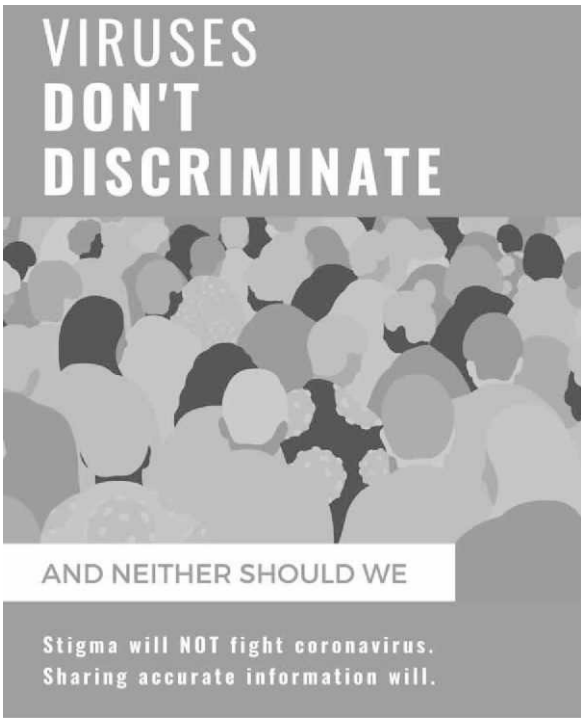
Comparison of efficacy of nifedipine and nitroglycerine in inhibiting uterine contractions for prolongation of pregnancy in preterm labour;Nifedipine is found to be more effective than Nitroglycerine.

REFERENCES

1. Howson C.P., Kinney M.V., Lawn J. March of Dimes, PMNCH, Save the Children, WHO; 2012. Born Too Soon: the global action report on preterm birth.
2. Songthamwat S, Na Nan C, Songthamwat M. InternationalJournal ofWomen's Health 2018;10: 317-323
3. Maternal and Newborn disparities Pakistan , Unicef Data: 2015
4. Diaz SH, Boeke CE, Romans AT Triggers of spontaneous preterm delivery- Why today? Paediatric Perinatal Epidemiology 2014 Mar:28(2):79-87
5. Hass D, Benjamin T, Sawyer R et all Short term tocolytics for preterm delivery- current perspective. International Journal of Women's Health 2014;6: 343-349
6. The use of Nifedipine in obstetrics: College Statement, C-Obs 15 1st Endorsed: July 2002 Current: June 2011 Review: June 2014 The Royal Australian and New Zealand College of Obstetricians and Gynaecologist
7. Robert Gasper, Judit Hajagos-Toth Calcium Channel Blockers as tocolytics: Principles of their actions, Adverse Effects and Therapeutic Combinations. Pharmaceuticals(Basel) 2013 Jun; 6(6): 689-699
8. WHO Reproductive Health Library. WHO recommendation on the use of tocolytic treatment for inhibiting preterm labour (November 2015). The WHO Reproductive Health Library; Geneva: World

Health Organization.

9. Haas DM, Imperiale TF, Kirkpatrick RW et all Tocolytic therapy: a mata analysis and decision analysis. Obst Gynecol 2009 Mar:113(3):584-94
10. Nankali A, Jamshidi P, Rezaei M. The effects of Glyceryl Trinitrate Patch on the Treatment of Preterm Labor: A single blind Randomised Clinical Trial Journal of Reproduction & Infertility 2014 Apr- Jun; 15(2):71-77
11. Smith GN, Walker MC, Ohlsson A, O'Brien K, Windrim R; Canadian Preterm Labour Nitroglycerin Trial Group. Randomized double-blind placebo-controlled trial of transdermal nitroglycerin for preterm labor. Am J Obstet Gynecol. 2007; 196(1): 37.e1-37.e378.
12. Shah K, Gupta B.D, Sharma R Dermal nitroglycerine patch in treatment of preterm labour. Journal of Biosciences and Medicines, 2015, 3, 82-90
13. Ross MG, Eden RD, Preterm labour. eMedicine/ Obstet and Gynecol 2009; 1-13.
14. Amorim MM, Lippo LA, Costa AA, Coutinho IC, Souza AS. Transdermal nitroglycerin versus oral nifedipine administration for tocolysis: a randomized clinical trial. Rev Bras Ginecol Obstet 2009; 31: 552-8.
15. Dhawle A, Kalra J, Bagga R, Aggarwal N. Nifedipine versus nitroglycerin for acute tocolysis in preterm labour: a randomised controlled trial. Int J Reprod Contracept Obstet Gynecol. 2013;2:61-6
16. Kashanian M, Zamen Z, Sheikhansari N. Comparison between nitroglycerin dermal patch and nifedipine for treatment of preterm labor: a randomized clinical trial. J Perinatol. 2014;34(9):683-7.
17. Sharma N, Rani S, Huria A, Chawla D. Oral nifedipine versus nitroglycerinepatch for tocolysis in preterm labour. Int J Reprod Contracept Obstet Gynecol 2019;8:174-8.
18. Ishaq N, Ishaq Z, Mushtaq A et all Comparative study of Tocolytic efficacy of Nifedipine and Nitroglycerine. J. Soc. Obstet. Gynaecol. Pak. 2017; Vol 7. No.2
19. Conde A, Romero R, Kusanovic J.P. Nifedipine for the management of preterm labour: A systematic review and meta analysis. Am J ObstetGynecol. 2011 Feb;204(2): 134.e1-134.20
20. Conde A, Romero R. Transdermal nitoglycerin for the treatment of Preterm labor: Asystematic review and meta analysis. Am J Obstet Gynecol. 2013 Dec; 209(6): 551.e1–551.e18.
21. Preterm labour and birth. Nice guideline. Published: 20 November 2015



EFFECT OF DIFFERENT PREBIOTICS ON LIPID PROFILE OF HIGH FAT FED RATS

Komal Iqbal,[1] Muniza Saeed,[2] Sana Rasheed Chaudhry,[3] Shagufta Khaliq,[4] Samita Yasmeen[5]

How to cite: Iqbal K, Saeed M, Chaudhary SR, Khaliq S, Yasmeen S. Effects of different probiotics on lipid profile of high fat fed rats. JAIMC. 2021; 19(1): 24-30.

Abstract

Background: Prebiotics are the components of food which are non digestible and improve health by promoting the survival of the selective bacterial species in the colon. Many studies have shown positive results about the effect of prebiotics on lipid profiles. This study was planned to compare the role of three prebiotics, galactooligosaccharides (GOS), fructooligosaccharide (FOS) and mannooligosaccharides (MOS) on the lipid profileof high fat fed rats and to see which one is better among the three.

Objective: To see the effects of three prebiotics, galactooligosaccharides (GOS), fructooligosaccharide (FOS) and mannooligosaccharides (MOS) on lipid profile of rats which were given high fat diet along with a prebiotic.

Methodology: Three weeks old forty male Sprague Dawley rats were seperated into five groups, with 8 rats in every group : (1) NC (Negative Control) group, fed on standard rat chow (2) PC (Positive control) group (high fat diet i.e. 40% beef tallow in standard rat chow) (3) GOS group (high fat diet containing 10% GOS) (4) MOS group (high fat diet supplemented with 10% MOS) (5) FOS group (high fat diet supplemented with 10% FOS). Their body weight was measured weekly. After 24 weeks blood samples were drawn and the rats were sacrificed and their liver weight was measured. Serumtriglycerides (TG), Total cholesterol (TC), high-density and low density lipoproteins cholesterol (HDL-C) were analyzed.

Results: All the three prebiotics were able to decrease the weight of experimental groups when they were compared to PC group. Least increase in body weight was observed on administration of MOS but a nonsignificant difference of ($p>0.05$) was seen. Liver weight of all treatment groups was lower as compare to PC group ($p=0.002$).

After 24 weeks total cholesterol, triglyceride, LDL, were lower in GOS, MOS and FOS group in comparison to PC group and a statistically significant difference of ($p < 0.05$) was seen. GOS and FOS group were able to decrease serum cholesterol significantly ($p=0.001$). Triglycerides were decreased significantly in all the experimental groups but FOS was able to decrease triglycerides more as compare to the other prebiotics. HDL was raised in the experimental group but it was statistically non significant.

Conclusion: Administration of Galacto oligosaccharide, Fructooligosassharide and Mono oligosaccharide significantly decreased lipid profile. MOS was better in reducing the body weight, liver weight and LDL. FOS is better in decreasing the cholesterol and triglyceride.

Key Words: Prebiotics, Obesity, Lipid profile.

1. Komal Iqbal
2. Muniza Saeed
3. Sana Rasheed Chaudhry
4. Shagufta Khaliq
5. Samita Yasmeen

1,2,3,5. Ameer Ud Din Medical College/ Post Graduate Medical Institute (PGMI) Lahore, Pakistan

4. Amna Inayat Medical College, Lahore, Pakistan

Correspondence:
Dr. Komal Iqbal, *Assistant Professor Physiology, Ameer Ud Din Medical College/ Post Graduate Medical Institute (PGMI) Lahore, Pakistan. E-mail: komaln69@gmail.com*

Submission Date: 16-10-2020
1st Revision Date: 18-11-2020
2nd Revision Date: 26-11-2020
Acceptance Date: 28-11-2020

One of the major causes of type 2 diabetes , fatty liver disease and heart disease is obesity (Dewulf et al., 2012). According to Arora and Sharma (2011) lack of balance between the intake of food, physical activity, and type of diet can result in obesity.

In the development of obesity and metabolic diseases gut microbiota plays a vital role. Alterations in intestinal microbiota composition has been seen in obese individual when compared with

lean subjects.[3] A reductions in Bacteroidetes and a comparative rise in the Firmicutes is associated with obesity.[4]

Probiotics are live microorganisms that support health benefits upon ingestion. They alter the composition of microbiata residing in the colon and improve the intestinal microbial balance. Limited amount of probiotic bacteria can be taken from the external source so the changes may be transient[5].

Prebiotics are the components of food which are not digested and improve health of the host. The intestinalmicrobiota composition is modified by adding prebiotic products in the diets as they improve the health of host by promoting the survival and activity of the selective bacterial species, which are already present in the colon[6]. As they are oligosaccharides in nature so they resist the activity of human digestive enzymes and undergo fermentation by bacteria in the caecum. Example of prebiotics includes inulin, fructooligosaccharide and galactooligosaccharides.[7]

Neither they gel in the gut nor do they change the viscosity of the intestinal contents. So their mechanism of action is different from other soluble fiber that form a gel-like emulsion which does not allow pancreatic lipase to hydrolyse fat. They affect thelipidmetabolism by inhibiting the synthesis of fatty acid.Prebiotics also increase the manufacturing of propionate a short chain fatty acid (SCFA), that down regulate a hepatic lipogenic enzyme, Fatty Acid Synthase (FAS).[8]

This study was planned to identify the most efficacious of the three prebiotics galactooligosaccharides (GOS), fructooligosaccharide (FOS) and mannooligosaccharides (MOS)on lipid profile of rats who were given high fat diet along with a prebiotic.

METHODOLOGY

The animal experimental study was carried out at Post Graduate Medical Institute Lahore. Three weeks old forty Male Sprague-Dawley rats were taken from University of Animal and Veterinary Sciences Lahore. The rats were kept in iron cages with natural day and night cycle at a temperature of 22-24 °C. They were acclimatized for a week with free provision of water and food. The rats were then seperated in five groups having 8 rats in each group.

Group 1- was Negative Control (NC) to which standard rat chow was given. Group 2-was Positive Control (PC) to which rats high fat diet (40% beef tallow in normal rat chow) was given.[9]

Group 3 (GOS), was given a high fat diet in which 10% GOS was added. Group 4 (MOS), rats were given a diet rich in fat added with10% MOS. Group 5 (FOS), were given diet rich in fat along with 10% of FOS.

Blood sample through cardiac puncture were collected from each rat after the end of 24 weeks and they were sacrificed. Serum was separated from the blood and stored at - 20 °C. Total cholesterol (TC), Triglycerides TG), high density lipoprotein-cholesterol (HDL-C) and low density lipoprotein-cholesterol (LDL-C) levels were analyzed.

Data was analysed by using IBM-SPSS, version 22. For normally distributed variables One-way ANOVA and Post Hoc Tuckey test were applied. For non-normally distributed variables, Kruskal Wallis test and Mann Whitney U test were applied. A p-value of < 0.05 was considered statistically significant.

RESULTS

In the first of study weight of rats in NC group was 64.22 g± 18.91g, PC was 63.55 g± 19.71 g, GOS group was 80.55g ± 15.70 g, MOS group was 68.55g ±14.66 g and FOS group was 75.11±16.55 g (Fig.1).

After 24 weeks mean weight of rats in NC group was 295.12g± 48.87 g, PC group was 347.75g ± 66.23 g, GOS group was 333.00 g± 51.88 g, MOS group was 312g±66.33 g and FOS group was 332.22 g ± 62.08 g. (Fig. 1). No significant difference was seen in the means of all groups by ANOVA ($p = 0.428$) (Fig.1)

No significant difference in body weight was seen among the groups by Post Hoc Tukey test.

Table 1: *Comparison of Body Weight Among the Groups by Post Hoc Tukey Test at the End of 24 Weeks Study Period*

VARIABLES n= 8	GROUP 1	GROUP 2	P VALUE
BODY WEIGHT (g)	NC	PC	0.417
	NC	GOS	0.717
	NC	MOS	0.980
	NC	FOS	0.641
	PC	GOS	0.988
	PC	MOS	0.757
	PC	FOS	0.996
	GOS	MOS	0.988
	GOS	FOS	1.000
	MOS	FOS	0.922

(Table 1)

n = no. of rats in a group. NC = Negative control, PC = Positive Control, GOS = Galacto oligosaccharide, MOS = Manno oligosaccharide, FOS = Fructo oligosaccharide

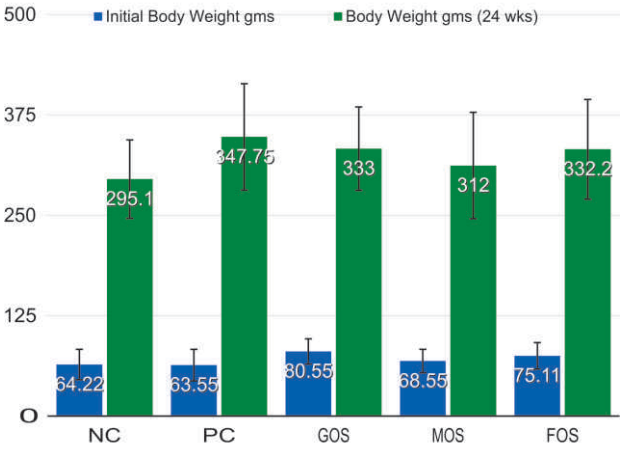


Figure-1: *Comparison of Body Weight (Mean ± SD) of Rats in all Study Groups at the Beginning and End of 24 Weeks Study Period*

After 24 weeks the rats were sacrificed and liver weight was measured. Liver weight of rats in NC group was 8.94 g ± 1.47 g, PC group was 13.48 g ± 2.62 g, GOS group was 12.4 g ± 1.57 g, MOS group was 11.64 g ± 1.96 g and in FOS group was 12.34 ± 2.45 g. (Fig.-2). Significant difference was found between the means of all groups by ANOVA (p= 0.002). Multiple comparisons by Post Hoc Tukey test revealed that liver weight of PC group was significantly higher when matched with NC group with a p = 0.001. Liver weight of treatment groups was also higher as compared to NC group. Difference was significant between NC and GOS (p = 0.015), NC and FOS (p = 0.017) but there was no significant difference between NC and MOS group (p = 0.099) showing that liver weight of MOS group were closer to NC group. When compared to PC group, liver weight of all treatment groups were lower as compare to PC group but multiple compa-risons of the three treatment group revealed that the difference was non significant amongst them (Table -2).

Significant difference (p=0.000) in serum total cholesterol level was seen among the groups by Mann Whitney U test (Table-2). Median (IQR) of NC group was 57.68 mg/dl (50.61-64.33), PC was 152.17mg/dl (132.84-169.47), GOS group was 101.23 mg/dl (93.99-114.49), MOS was 97.09 mg/dl (79.02-137.42), FOS group was 90.88 mg/dl (82.29-112.00) (Fig.- 3).

Significant difference (p = 0.000) in serum total cholesterol level was seen between the means of all the groups by Kruskal Wallis test.

Table 2: *Comparison of Liver Weight Among the Groups by Post Hoc Tukey Test at the End of 24 Weeks Study Period*

Parameter n = 8	Group	Group	*p* Value
Liver weight (g)	NC	PC	0.001***
	NC	GOS	0.015**
	NC	MOS	0.099
	NC	FOS	0.017**
	PC	GOS	0.878
	PC	MOS	0.422
	PC	FOS	0.863
	GOS	MOS	0.930
	GOS	FOS	1.000
	MOS	FOS	0.940

NC = Negative control, PC = Positive Control, GOS = Galacto oligosaccharide, MOS = Manno oligosaccharide, FOS = Fructo oligosaccharide.

Comparison of serum cholesterol by Mann Whitney U test revealed that serum Triglycerides of PC group was significantly higher as compared to that of NC group with p = 0.001. Difference was significant between PC and GOS (p =0.021), PC and MOS (p = 0.046) and PC and FOS group (p = 0.001)

(Table 3).

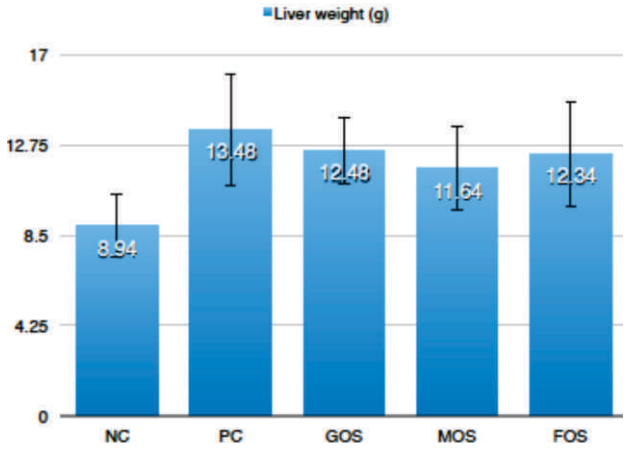


Figure-2: *Liver Weight (Mean ± SD) of Rats in all Study Groups at the End of 24 Weeks Study Period.*

Median (IQR) of triglycerides of rats in NC group was 106.41mg/dl (80.50mg/dl-114.11mg/dl) PC group was 421.10 mg/dl (353.20mg/dl-495.87 mg/dl), GOS group was 296.96 mg/dl (146.33mg/dl-379.36mg/dl), MOS group was 300.91 (248.15 mg/dl-354.67mg/dl) and FOS group was 205.50 mg/dl(183.70mg/dl-297.24mg/dl) (Fig-4).

Mean HDL cholesterol of rats in NC group was 9.92mg/dl ± 0.55mg/dl, PC group was 11.38 mg/dl ± 3.80mg/dl GOS group was 11.80 mg/dl ± 5.75mg/dl,

Table 3: *Comparison of Serum Cholesterol Levels among the groups by Mann Whitney U test at the end of 24 Weeks Study Period*

Parameter n = 8	Group	Group	*p* Value
Serum Cholesterol (mg/dl)	NC	PC	0.001***
	NC	GOS	0.001***
	NC	MOS	0.001**
	NC	FOS	0.000***
	PC	GOS	0.001***
	PC	MOS	0.027*
	PC	FOS	0.001***
	GOS	MOS	0.916
	GOS	FOS	0.431
	MOS	FOS	0.674

*p <0.05 significant ***p = 0.00 highly significant
n = no. of rats in a group. NC=Negative control,
PC=Positive Control, GOS=Galactooligosaccharide,
MOS=Manno oligosaccharide, FOS=Fructooligosaccharide

MOS group was 14.99mg/dl ± 4.60mg/dl and FOS group was13.25 ± 3.19 (Fig.-5). No significant difference was found between the means of all groups by ANOVA (p= 0.136).

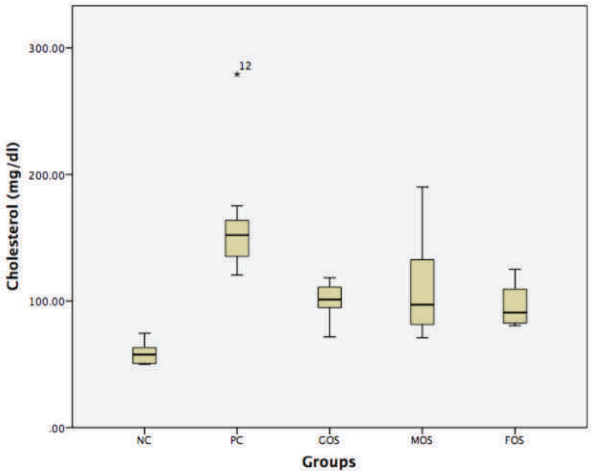


Figure- 3: *Serum Cholesterol Levels (Median IQR) of Rats in all Study Groups at the End of 24 Weeks Study Period.*

Median (IQR) of LDL cholesterol of rats in NC group was 26.84 mg/dl (24.03mg/dl-32.75mg/dl),

Table 4: *Comparison of Serum Triglycerides Levels Among the Groups by Mann Whitney U Test at the End of 24 Weeks Study Period*

Parameter n = 8	Group	Group	*p* Value
Serum Triglycerides (mg/dl)	NC	PC	0.001***
	NC	GOS	0.000***
	NC	MOS	0.001***
	NC	FOS	0.001***
	PC	GOS	0.021*
	PC	MOS	0.046*
	PC	FOS	0.001***
	GOS	MOS	0.674
	GOS	FOS	0.345
	MOS	FOS	0.093

*p <0.05 significant ***p = 0.001 highly significant
n = no. of rats in a group. C= Negative control,
PC = Positive Control, GOS = Galacto oligosaccharide,
MOS = Manno oligosaccharide, FOS= Fructo oligosaccharide.

PC group was 53.02 mg/dl (38.36mg/dl-81.01 mg/dl) GOS group was 26.34 mg/dl (19.18mg/dl-49.67mg/dl), MOS group was 26.46 mg/dl (15.86 mg/dl-54.14mg/dl) and FOS group was 34.42 mg/dl

(26.41mg/dl-49.94mg/dl) (Fig.-6). Significant difference was found between the means of all groups by Kruskal Wallis (p = 0.035)

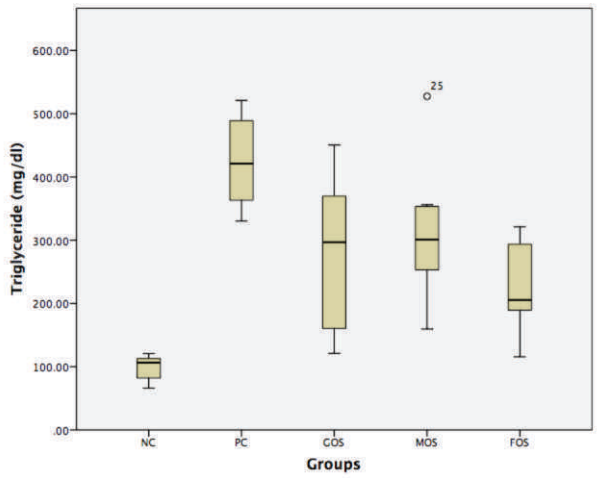


Figure-4: *Serum Triglyceride Levels (Median IQR) of Rats in all Study Groups at the end of 24 Weeks Study Period*

NC=Negative control, PC=Positive Control, GOS=Galactooligosaccharide, MOS=Manno oligosaccharide, FOS=Fructo oligosaccharide.

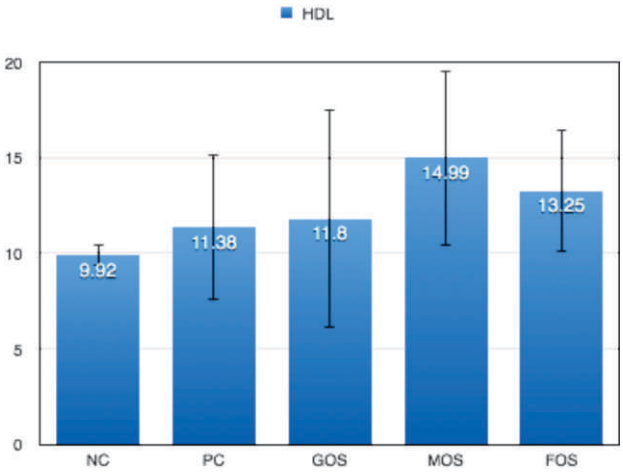


Figure-5: *Serum HDL Cholesterol Levels (Mean ± SD) of Rats in all Study Groups at the End of 24 Weeks Study Period*

° is an outlier. , NC=Negative control, PC=Positive Control, GOS=Galacto oligosaccharide, MOS=Manno oligosaccharide, FOS=Fructo oligosaccharide

DISCUSSION

Nondigestible oligosaccharides (NDOs) show a prebiotic effect. They can be used as a dietary source for the control of obesity and metabolic syndrome. Many animal studies have revealed that they regulate body weight, dyslipidemia, insulin resistance, hypertension, and liver steatosis.[10]

Many studies have reported antiobesity effects of prebiotics in rats.[11,8] Body weight was measured every weekly. The body weight was decreased by addition of the three prebiotics as compare to PC group. Least increase in body weight was observed by administration of MOS andt he difference was statistically non significant (p = 0.428). There are controversialreports regarding inhibition in body weight gain by prebiotics. Cani et al. administered FOS along with diet rich in fat to rats for 14 weeks and reported a reducedbody weight gain.[11] However Parnell and Reimeradministered FOS and inulin along with high fat diet to rats for 10 weeks and reported no difference onbody weight gain.[4] Similarly Smith et al. reported a nonsignificant difference in body weight with MOS in 12 weeks study period on mice.[12]

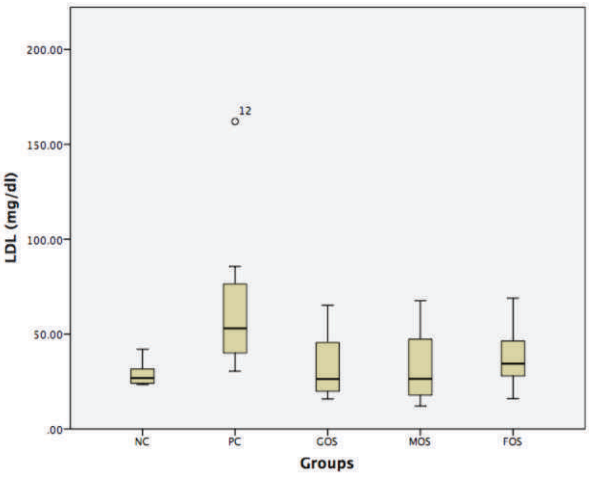


Figure-6: *Serum LDL Cholesterol {Median (IQR)} of Rats in all Study Groups at the End of 24 Weeks Study Period*

A significant decrease in liver weight was seen in this study (p = 0.002) by administration of GOS, MOS and FOS group as compare to PC group. Similar results have been seen by the study conducted on rats by An et al. by giving a probiotic with high fat diet.[9] Manno oligosaccharide (MOS) was able to decrease the liverweight significantly as compare to

the other two prebiotics in this study. Kumao et al. administered MOS in liquid coffee to healthy adults and their study showed an increased in the amount of excreated fat and decreased fat utilization after the administration of 3gms MOS per day.[13]

This study showed a decrease in serum cholesterol by the administration of all the three prebiotics ($p<0.001$).Improvement in lipid profiles through administration of either probiotics[9] or a prebiotic (GOS)have been reported in some studies.[10] In 2013 Vulevic administered GOS to overweight individuals and found a significant decrease in lipid profile.[14]

A study on hypercholesterolemic rat model by Parnell and Reimer showed that there is a significant decrease in cholesterol level after the administration of Inulin and FOS. [8]

Prebiotics act as an ideal substrate for bifidobacteria and lactobacilli which are the health promoting bacteria in the colon.[15] There are many mechanisms involved in lowering the serum cholesterol, i,e enzymes involved in cholesterol synthesis are inhibited by the fermentation products of lactic acid bacteria.[9] Production of propionate which is a short chain fatty acid (SCFA) is increased by prebiotics. Propionate down regulate a hepatic lipogenic enzyme, Fatty Acid Synthase (FAS).[8]

The bacteria also binds with the cholesterol thus inhibiting its absorption back into the body. These bacteria also help in the elimination of cholesterol by interfering with the reuse of bile salts. This results in consumption of body cholesterol for the resynthesis of bile salts.[9] An enzyme bile salt hydrolase excreted by some bacterial species, leads to increased excretion of bile in feces. Deconjugation and precipitation of bile acids in enterohepatic circulation causes their excretion from the feces by bacteria thus reducing serum cholesterol concentration.[16]

Adminstration of all the three prebiotics showed a significant decrease in triglyceride levels with a ($p < 0.001$). Decreased level of triglycerides in response to dietary inulin has been reported by Cieslik.[17] Whereas in another study Delzene suggested that FOS decreased the levels of triglycerides in Very Low Density Lipoproteins (VLDL).[18]

The mechanism by which FOS lowers the triacylglycerol levels is through the reduction of hepaticdenovo fatty acid synthesis. It inhibits the enzymes involved in lipid synthesis namely acetyl-CoA carboxylase, fatty acid synthase, malic enzyme, ATP citratelyase, and G6PD. Fatty acid synthase (FAS) is among the main enzymes that control lipogenesis.[18]

All the three prebiotics significantly decreased the lipid profile but a marked reduction by FOS was seen when compared with PC group. A significant decrease in cholesterol ($p = 0.001$) and triglycerides ($p= 0.001$) was seen after the administration of FOS. Whereas MOS showed a decrease in LDL-C ($p= 0.027$). HDL-C was highest in MOS treated group but comparison with PC group showed a non significant difference.

CONCLUSION

Administration of Galacto oligosaccharide, Fructooligosassharide and Mono oligosaccharide significantly decreased lipid profile. MOS was better in reducing the body weight, liver weight and LDL. FOS was better in decreasing the cholesterol and triglyceride.

REFERENCES

1. Dewulf EM, Cani PD, Claus SP, Fuentes S, Puylaert PG, Neyrinck AM et al. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. Gut 2013 Aug62(8): 1112–1121.
2. Arora T, Sharma R. Fermentation potential of the gut microbiome: implications for energy homeostasis and weight management. Nutrition reviews. 2011 Feb 1;69(2):99-106.
3. Sanz Y, Santacruz A, Gauffin, P. Session 8: Probiotics in the defence and metabolic balance of the organism Gut microbiota in obesity and metabolic disorders. Proceedings of the Nutrition Society. 2010 Jun69(3): 434-441.
4. Parnell JA, Reimer RA. Prebiotic fibres dose-dependently increase satiety hormones and alter

Bacteroidetes and Firmicutes in lean and obese JCR: LA-cp rats.Br JNutr. 2012 Feb 107(04): 601-613.

5. Fujimura KE, Slusher NA, Cabana MD, Lynch SV. Role of the gut microbiota in defining human health. Expert Rev anti-infectTher. 2010 Apr8(4): 435-454.
6. Roberfroid MB. Prebiotics and probiotics: are they functional foods?Am J ClinNutr . 2000 Jun 71(6): 1682-1687.
7. Wallace TC, Guarner F, Madsen K, Cabana MD, Gibson G, Hentges E et al. Human gut microbiota and its relationship to health and disease. Nutrition Reviews2011 Jun. 69(7): 392-403.
8. Parnell, J.A. and Reimer, R.A., 2009. Effect of prebiotic fibre supplementation on hepatic gene expression and serum lipids: a dose-response study in JCR:LA-cp rats. Br. J. Nutr., 103(11): 1577-1584.
9. An HM, Park SY, Lee DK, Kim JR, Cha MK, LeeSW et al. Antiobesity and lipid-lowering effects of Bifidobacterium spp. in high fat diet-induced obese rats. Lipids Health Dis., 2011 Jul. 10 (1): 116-124.
10. Vulevic J, Juric A, Tzortzis, G. Gibson GR. A mixture of trans-galactooligosaccharides reduces markers of metabolic syndrome and modulates the fecal microbiota and immune function of over-weight adults. J. Nutr, 2013 Mar 143(3): 324-331
11. Cani, P.D., Neyrinck, A.M., Fava, F., Knauf, C., Burcelin, R.G., Tuohy, K.M.,Gibson, G.R. and Delzenne, N.M., 2007. Selective increases of bifido-bacteria in gutmicroflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. Diabetologia, 50(11): 2374-2383.
12. Smith, D.L., Nagy, T.R., Wilson, L.S., Dong, S., Barnes, S. and Allison, D.B., 2010. The effect of mannan oligosaccharide supplementation on body weight gain and fat accrual in C57Bl/6J mice. Obesity, 18(5): 995-999
13. Kumao, T., Fujii, S., Asakawa, A., Takehara, I. and Fukuhara, I., 2006. Effect of coffee drink containing mannooligosaccharides on total amount of excreted fat in healthy adults. Journal of health science, 52(4): 482-485.
14. Vulevic J, Drakoularakou A, Yaqoob, P., Tzortzis, G. Gibson GR., 2008. Modulation of the fecal micro-flora profile and immune function by a novel trans-galactooligosaccharide mixture (B-GOS) in healthy elderly volunteers. Am. J. Clin. Nutr., 2008 Nov 88(5): 1438-1446.
15. Jackson KG, Lovegrove JA, 2012. Impact of probiotics, prebiotics and synbiotics on lipid metabolism in humans. Nutrition and Aging. 2012 Nov1(3, 4): 181-200.
16. Xie N, Cui Y, Yin YN, Zhao X, Yang JW, Wang ZG et al. Effects of two Lactobacillus strains on lipid metabolism and intestinal microflora in rats fed a high-cholesterol diet. BMC Complement Altern. Med..201111(1):1.
17. Cieślik E, Pisulewski PM, 2005. Effects of fructooligosaccharides and long-chain inulin on serum lipids in rats. Pol. J. Food Nutr. Sci. 2005 14(2005): 437-441.
18. DelzenneNM, Kok N, 2001. Effects of fructans-type prebiotics on lipid metabolism. Am J Clin Nut 2001 Feb 73(2): 456-458.

AUTOPSY OF UNIDENTIFIED BODIES; DEATH IN SILENCE

Saima Tahir,[1] Faiza Muneer,[2] Aamna Zafar,[3] Izza Rehan,[4] Pervaiz Zareef[5]

How to cite: Tahir S, Muneer F, Zafar A, Rehan I, Zareef P. Autopsy of unidentified bodies: death in silence. JAIMC. 2021; 19(1): 31-35.

Abstract

Background: Medico legal autopsies are conducted in all cases of deaths in suspicious circumstances and unidentified bodies. Establishing the identity becomes a challenging task in these cases, rest aside finding the cause of death.

Objective: The present study is carried out to highlight the demography of unidentified bodies in the metropolitan city Lahore, Pakistan, on whom autopsies were conducted, for establishing identification and cause of death.

Methodology: The present study is a 3year retrospective study that took place from January2017 to December2019 at Department of Forensic Medicine and Toxicology, Lahore General Hospital. All the cases of unidentified bodies are included in this study. Data is collected from police docket, autopsy report, hospital records and reports from Punjab Forensic Science Agency.

Results: The present study is undertaken in Lahore General Hospital, Department of forensic medicine and toxicology to find the pattern of death in cases of unidentified bodies and the efforts made for their identification by medical and non-medical persons. Number of unidentified bodies brought for autopsy is 26% of the total autopsies done in Lahore General Hospital, that is an alarming rate in itself, peak age of deceased belongs to the age group 31- 40 years with male predominance. Whereas, in cases of feticide, female predominance is observed. Coronary arteriosclerotic changes are observed in majority of cases, as leading cause of death.

Conclusion: For identifying the maximum dead bodies, NADRA should be actively involved in all such cases and there is dire need to stream line the efforts of police.

Key Words: Autopsy, death, unidentified body

Unidentified decedent or unidentified person is a term used to describe a corpse of a person whose identity cannot be established by police and medical examiners.[1] A body may go unidentified due to death in a state where the person was unrecorded, in advanced state of decomposition or major facial injuries.[2)]

One of the primary objectives of Medicolegal autopsy is identification of the deceased in unidentified cases.[3] Body identification is a subfield of Forensic science wherein investigators need to identify a body. Forensic purposes are served by rigorous scientific techniques, but these are generally preceded by simply asking bystanders or other persons for the victim's name.[4] If a body is not badly decomposed or damaged, two persons (or one) who knew the deceased well should visually confirm the identity.

Usually, bodies are identified by comparing their usual fingerprints and dental characteristics. DNA is considered the most accurate.[5] It is often obtained through hair follicles, blood, tissue and other biological material.[6] In addition forensic photography, evidence of surgery, breaks and fractures, and height and weight may help in identification.[7] A medical examiner will often be involved with identifying a body.

1. Saima Tahir
2. Faiza Muneer
3. Aamna Zafar
4. Izza Rehan
5. Pervaiz Zareef

1-5. Forensic Medicine, PGMI, Lahore

Correspondence:
Dr. Saima Tahir, Department of Forensic Medicine, PGMI, Lahore

Submission Date: 21-10-2020
1st Revision Date: 15-11-2020
2nd Revision: 26-11-2020
Acceptance Date: 30-11-2020

METHODOLOGY

A total of 277 dead bodies were brought for postmortem examination in Forensic Medicine Department, Lahore General Hospital from January 2016 to December 2019. 72 autopsies on unidentified dead bodies were performed which was 26% of the total autopsies.

RESULTS

Only 11 (15.3%) unidentified dead bodies were female and remaining 61 (84.7%) were male bodies as shown. In 2017 male to female ratio was 10:1, in 2018 this ratio was 4:1 and in 2019 it was dropped to 3:1 as shown in bar chart.

Maximum bodies were found to be in age group of 31-40 yrs, followed by 21-30 yrs and then 41-50 yrs. Least number of bodies was one in age group less than 10 yrs (Table1).

Shadman police station brought 13 bodies from their area (18.1%) that was maximum, and 11 bodies were from Ichhra (15.3%). Police station Defence A was the last in this list of 13 police stations that are being covered by LGH, with one case (1.4%) (Table 2). January is the month, in which 12 (16.7%) unidentified bodies were autopsied upon, in October 10 cases (13.9%) were brought, followed by July with 9 cases (12.5%)(Table 3).

Out of these 72 unidentified bodies, 9 were

Table 1: *Age Wise Distribution of Unidentified Cases*

Ages	2017 (n=34)		2018 (n=18)		2019 (n=20)		Total Cases (72)	
	No	%	No	%	No	%	No	%
Less than 10 yrs	2	5.7	0	0	0	0	2	2.9
11 to 20 yrs	0	0	0	0	1	5	1	1.4
21 to 30 yrs	4	11.7	2	11.1	6	30	12	16.7
31 to 40 yrs	9	26.5	5	27.8	1	5	15	20.8
41 to 50 yrs	5	14.7	3	16.7	4	20	12	16.7
51 to 60 yrs	5	14.7	3	16.7	3	15	11	15.3
More than 60 yrs	5	14.7	2	11.1	3	15	10	13.9

Table 1: *Police Station Involved*

Sr. No	Police Station	2017 (n=34)		2018 (n=18)		2019 (n=20)		Total Cases (72)	
		No	%	No	%	No	%	No	%
1.	**Shadman**	8	23.5	3	16.7	2	10	13	18.1
2.	**Ichra**	4	11.7	3	16.7	4	20	11	15.3
3.	**Race Course**	5	14.7	0	0	4	20	9	12.5
4.	**South Cantt**	5	14.7	1	5.5	1	5	7	9.7
5.	**Mustafabad**	2	5.8	3	16.7	0	0	5	6.9
6.	**North Cantt**	3	8.9	2	11.1	0	0	5	6.9
7.	**Ghalib Market**	0	0	2	11.1	2	10	4	5.5
8.	**Ghaziabad**	1	2.9	0	0	3	15	4	5.5
9.	**Gulberg**	1	2.9	2	11.1	1	5	4	5.5
10.	**Milat Park**	1	2.9	1	5.5	1	5	3	4.1
11.	**Defence B**	2	5.8	0	0	1	5	3	4.1
12.	**Defence C**	1	2.9	1	5.5	1	5	3	4.1
13.	**Defence A**	1	2.9	0	0	0	0	1	1.4

Table 3: Month Wise Distribution of the Cases

Month	2017 (n=34)		2018 (n=18)		2019 (n=20)		Total Cases (72)	
	No	%	No	%	No	%	No	%
January	10	29.4	1	5.5	1	5	12	16.7
February	0	0	1	5.5	2	10	3	4.2
March	3	8.8	2	11.1	2	10	7	9.7
April	2	5.8	2	11.1	4	20	8	11.1
May	0	0	1	5.5	1	5	2	2.7
June	2	5.8	3	16.7	1	5	6	8.3
July	5	14.7	3	16.7	1	5	9	12.5
August	2	5.8	1	5.5	4	20	7	9.7
September	3	8.8	2	11.1	1	5	6	8.3
October	5	14.7	2	11.1	3	15	10	13.9
November	2	5.8	0	0	0	0	2	2.7
December	0	-	0	0	0	0	0	0

fetuses of age group ranging from 20 x weeks to 40 x weeks of gestation, found during this period of three years from different police station areas of Lahore. 2 fetus had hospital tags tied on their wrists and 5 were diagnosed as live born and 5 were confirmed as still born (Table 4).

Maximum time elapsed before autopsy was 2 x weeks in 45 cases (62.5%). It took 3 x weeks in case of 15 (20.8%) unidentified bodies and 4 x weeks in case of 9 (12.5%) bodies. This time was taken by police to complete its work up and formalities before requesting autopsy (Table 5).

Both Histopathological and chemical examination was done in about 54.2% cases and only chemical examination was performed in 12.5% of cases. On basis of these reports, cause of death was found to be natural diseased processes like coronary arteriosclerosis, TB, hepatitis, pneumonia and renal tubular degenerative disease in 30 cases. Among these 30 cases, 12 were drug abuser too. Most common disease was coronary arteriosclerosis that was present in 17 cases whereas 4 of them were found to be drug abusers too. 10 more cases of drug abuse were detected on chemical examination with morphine being the commonest drug of abuse, amongst others were nordiazepam, tramadol, ethanol and nicotine. Cause of death in 8cases was brain damage due to road traffic accidents. No drug or disease was detected in 7 cases after histopathology and chemical examiner reports while in 5 cases, reporting was not possible due to autolysis. Phosphine was detected in one case and 9 were still waiting for results from PFSA (Table 6).

Sternum was taken for DNA analysis and two identification marks were noted by medicolegal

Table 4: Feticide Cases

No.	Age	Sex	Birth tags	Live born /still birth	Police station
1	20-24wks	F	_ve	still birth	Millat park
2	20-24wks	Unrecog-nizable	_ve	still birth	Def C
3	30-36wks	M	+ve	Live born	South cantt
4	32-36wks	F	_ve	still birth	Gulberg
5	34-36wks	M	+ve	Live born	Def B
6	36-38wks	F	_ve	live born	Ghalib market
7	36-39wks	F	_ve	Live born	Ghazi abad
8	36-40wks	M	_ve	Live born	Gulberg
9	40wks	F	_ve	still birth	Def C

Table 5: Time Elapsed Before Post Mortem

Days	2017 (n=34)		2018 (n=18)		2019 (n=20)		Total Cases (72)	
	No	%	No	%	No	%	No	%
0 to 7	11	32.3	8	44.4	3	15	22	30.5
8 to 14	13	38.2	5	27.7	5	25	23	31.9
15 to 21	5	14.7	5	27.7	5	25	15	20.8
22 to 28	4	11.7	0	0	5	25	9	12.5
29 to 35	1	2.9	0	0	1	5	2	2.7
More than 35	0	0	0	0	1	5	1	1.4

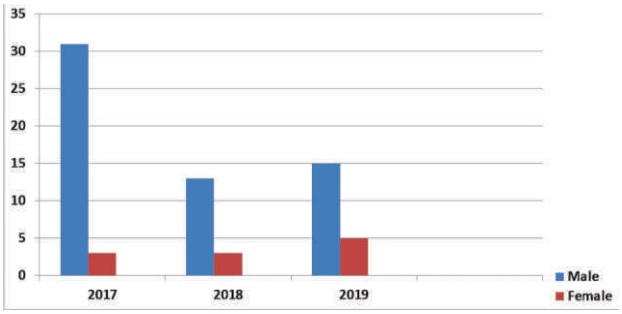
Table 6: Cause Of Death According To Histopathology And Chemical Examiner Reports

Sr. No.	Results of histopathology and chemical examiner reports	No of Cases
1.	Natural causes of death	31
2	Drug abuse leading to death	10
3	Results awaited	9
4	Brain injury due to road traffic accidents	9
5	No drug /disease detected	7
6	Autolysis	5
7	Phosphine detected	1

Table 7: Methods Of Identification Used

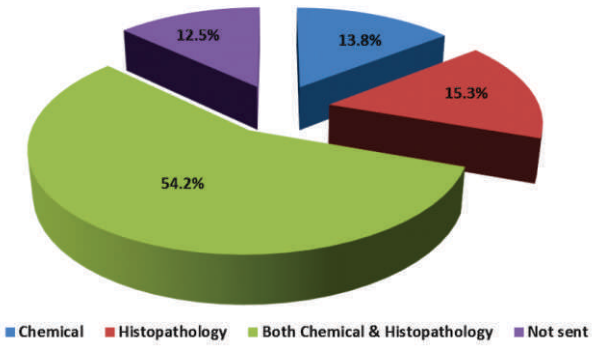
1	Two points of ID noted	MLO	100%
2	Fingerprints taken	Police	98.6%
3	Sternum for DNA	MLO	100%
4	Ads in newspaper	Police	100%
5	Itlaa e shor o ghoogha	Police	100%

officer in each case for the purpose of identification.



Ads were given by police in local newspapers and fingerprinting was done in all cases except in one body that was found to be mutilated with no arms and legs (Table 7).

MALE AND FEMALE



CASES SENT FOR CHEMICAL / HISTOPATHOLOGY ANALYSIS

DISCUSSION

Unidentified bodies became a focus of public attention in cases of mass disaster; otherwise these are hardly followed and sorted out. In Britain, a useful booklet on the role of the forensic pathologists in mass disaster is available[8] but no such literature is published for individual unclaimed unidentified bodies. This study was conducted in one of the major metropolitan cities of Pakistan, Lahore and percentage of unidentified was found to be 25%. A study was done in KEMU, Lahore where this percentage was more than 50% (401/ 785)[9] but in a similar study done in Faisalabad, unidentified autopsies were 13%[10] of the total autopsies. On the other hand this rate was 80% in US.[11]

On chemical examination, drugs of abuse were present in 22 cases, and it can be correlated with the areas where maximum cases were found as 31% cases were from Shadmann and Ichhra only. According to this study, male predominance was observed as was found in other two studies done in Lahore and Faisalabad.[9,10] In our country, males are the bread winner of the family and they have to travel to the other cities for job and at times even families are unaware of their whereabouts, so maximum number of bodies were in age group 31 to 40 years.

In present study, in 31% cases, cause of death was natural diseased processes. These findings are not consistent with the study done in Faisalabad where IHD was present in 2cases only. On the other hand, cause of death in two studies done in India by Ajay Kumar[12] and Chattypadhay[13] 50%cases were recognized to be due to natural causes.

For the purpose of identification, police gave ads in dailies and hue and cry appeals were made in the nearby areas where these bodies were found. Sternum was taken in 100% for DNA and fingerprints were also taken from all ten fingers but unfortunately no match was found. There is dire need to improve this area and local administration should keep the records of their inhabitants including the vagabonds, street beggars and destitute homeless persons. Request for autopsy was put forward only

after exhaustion of these efforts by police, it took mostly 8 to 14 days.

CONCLUSION

It is a common observation that in case of accidents or casualties on road, crowd gathered before arrival of police and anyone take the wallet or phone of the dead or seriously injured person thus depriving him from ID card and other possible means of identification. Mass media campaign should be launched to make people aware of the consequences of such inhumane act and police should be more vigilant in making identification possible at the time and place of such incident.

Dental data, old injury marks, tattoo marks and clothing should be noted and photographed and made public on social media to involve maximum people. It is the last right of every person to be buried by his loved ones and if possible, legislation can be done to make every possible attempt to identify the unclaimed dead bodies.

REFERENCES

1. "Resolved cases" doenelwork org. the doe network archieved from the original on 22nd october2014, retrieved 18 October 2014
2. "From flourishing life to dust- the natural cycle" mummies of the world Ed alfried wieczorek and wilfried rasendalh first ed 2010 28 print .
3. Jayaprakash pt singh B hassan NFN Aziz RA yusop m computer aided video superimposition device- a novel contribution to skull based identification in Malyasia. Health environ j 2010.
4. "death investigation- the graveyard shift" leelofland.com. Retrieved 6 April 2015.
5. Claridge, Jack (10 December 2014). "'identifying the victim" Explore Forensics. Retrieved 1 January 2015
6. "8 body parts forensic scientist use to ID a body". Forensic Science Technician. 2015. Retrieved 1 January 2015
7. Valk, Diana (18 November 2013). "3 ways to identify a body when DNA is not an option" Forensics Outreach. Retrieved 1 January 2015
8. Busuttil A,Jones JSP, Green MA, (eds). Major Disasters, the Pathologist's role. London: Royal College Of Pathologists, 2000, p.49
9. Audit of autopsies 2016, A Retrospective, Observational study. KEMU
10. Muhammad Naeem, Humaira Arshad, Mobin Inam Pal. Pattern of cause of death and injuries in unknown dead bodies, APMC 2018; 12(1):12-5
11. Paulozzi LJ, Cox CS, Williams DD, Nolte KB. John and Jane Doe: The epidemiology of unidentified decedents. J For Sci. 2008;53(4):922-27.
12. Ajay kumar et al, cause of death in John Doe and Jane Doe: A 5Y ear review, journal of clinical and diagnostic research. 2014 Aug, Vol-8(8): IE01-IE04
13. Chattopadhyay S, Shee B, Sukul B. Unidentified bodies in autopsy – A disaster in disguise. Egyptian Journal of Forensic Sciences. 2013; 3(4):112-15.

KNOWLEDGE, ATTITUDE AND PRACTICES REGARDING THE CONTROL OF BLOOD GLUCOSE LEVEL AMONG THE RESIDENTS OF MUSLIM TOWN, FAISALABAD

M. Maaz Alam,[1] Musharaf Arif,[2] Ehsan Ahmad,[3] Sumera Badar Ehsan,[4] Abdul Rafae Faisal,[5] Pramod Singh,[6] Muhammad Abdullah[7]

How to cite: Alam MM, Arif M, Ahmad E, Ehsan SB, Faisal AR, Singh P, et al. Knowledge, attitude and practices regarding the control of blood glucose level among the residents of Muslim town, Faisalabad. JAIMC. 2021; 19(1): 36-39.

Abstract

Objectives: This descriptive/cross-sectional research was undertaken to study the demographic details of the participants and their knowledge, attitude and practices regarding control of blood glucose.

Methodology: The KAP (Knowledge, Attitude and Practices) of the general public of Muslim Town, Faisalabad were studied during March 2020 by using a structured questionnaire. The study was conducted among 69 residents of Muslim Town, Faisalabad. Non-probability sampling was employed. All the participants were briefed about the aims of this study. Written or oral consent were taken before filling the questionnaire. Confidentiality was strictly maintained. Questions by the participants were encouraged and entertained. After collection of data, it was compiled on Microsoft Excel 2016 and analysed using R v. 4.0.2.

Results: Out of 69 participants, there were 53(76.81%) males and 16(23.19%) females. Most of the participants belonged to the age group of 41-60 (36.23%) followed by the age group of 26-40 (26.09%). Mean knowledge score of the participants was 5.79± 2.6, while mean attitude and practices score was found to be 2.61± 1.9. The level of knowledge was low in 21.7%, average in 37.6 % and good in 40.6 % of the participants. The attitude and practices scores consisted of 49.3% of the respondents scoring in the poor category and 33.3% falling in average category.

Conclusion: The adequate knowledge about blood sugar control did not translate into proper and useful attitudes and practices even for those who scored well. The modification of the approach and attitudes towards education on diabetes is the need of the hour.

Key Words: Diabetes, cross-sectional, blood sugar, KAP, knowledge, attitude and practices.

Diabetes Mellitus is a metabolic disorder characterized by chronic hyperglycaemia due to absolute or relative deficiency or diminished effectiveness of circulating insulin.[1] There are three main types of DM: type 1, type 2 and gestational diabetes. People with type 1 DM produce very little or no insulin at all and it is called insulin dependent diabetes mellitus (IDDM). Type 2 diabetes mellitus used to be called non-insulin (NIDDM) or adult-onset diabetes mellitus and accounts for at least 90% of all the case of diabetes. GDM is a form of diabetes consisting of high blood glucose level during pregnancy.[2]

The normal range of blood glucose is 70-120 mg/dl before meals and under 140mg/dl after meals. The self-monitoring of blood glucose (SMBG) for diabetes patients is clinically recommended.[3] SMBG is a crucial element of contemporary therapy for DM. Patient self-care behaviour includes following a diet plan, taking medication, exercising regularly and periodic testing of blood glucose. All these factors are pivotal in diabetes control.[4] Since diabetes mellitus is a serious health problem, it requires medical care, patient self-management, education

1. M. Maaz Alam
2. Musharaf Arif
3. Ehsan Ahmad
4. Sumera Badar Ehsan
5. Abdul Rafae Faisal
6. Pramod Singh
7. Muhammad Abdullah

1-7. Faisalabad Medical University, Faisalabad.

Correspondence:
Dr. Pramod Singh, Faisalabad Medical University, Faisalabad. *singhutd66@gmail.com*

Submission Date: 20-10-2020
1st Revision Date: 18-11-2020
Acceptance Date: 28-11-2020

and adherence to prescribed medication to reduce the risk of long-term complications. The knowledge of self-care leads to meaningful patient contribution in the management of their lives and control of their disease through a tight schedule of blood glucose and urine sugar monitoring, medication and adjustment to dietary condition.[5]

In the last two decades, the prevalence of DM has dramatically increased in many parts of the world and the disease is now a world-wide public health problem. The number of people suffering from DM is projected to rise from 171 million in 2000 to 366 million in 2030.[6] In the 21st century, our lives are very different from the ones our ancestors lived. We have become increasingly inactive and lead sedentary lives.[7] Some of these causes include desk work, life stressors and conveniences of technology. Additionally, the food markets have been inundated with the mass production of cheap fast food that appeals to the modern-day consumer. The combination of sedentary and busy lifestyles with readily available, calorie-rich processed foods has resulted in a myriad of medical problems that have become endemic across developed countries in the world.[8]

METHODOLOGY

The study used a cross-sectional study design and a structured questionnaire was used to collect data from 69 residents of Muslim Town, Faisalabad. Non-probability convenient sampling technique was utilized for selection of sample residents. The data so obtained was analysed using Microsoft Excel version 2016. The survey comprised of 20 questions which were selected for gathering information about socio-demographic details, knowledge, attitude and practices related to diabetes. Moreover, 9 questions were designed to reveal information about knowledge of risk factors, exercise, diet, smoking and effect of sugar intake on diabetes. Additionally, 6 questions enquired about attitude and preventive practices. Each correct response was given a score of 1, while an incorrect response scored zero. Knowledge, Attitude and Practices scores, their mean (X) and standard deviation (s) were calculated for description and analysis of data. Data on KAP (Knowledge, Attitude and Practices) among various socio-demographics were analysed for comparative study.

RESULTS

Out of 69 participants, there were 53(76.81%) males and 16(23.19%) females. Most of the participants belonged to the age group of 41-60 (36.23%) followed by the age group of 26-40 (26.09%). Only 7.25% participants belonged to the age group of 60 and above. Most of the people had acquired higher education (87%), 7% had passed matriculation, 3% participants had primary level of education and 3% participants were illiterate. 62 participants (89.86%) had a positive family history of diabetes.

Table 1: *Age Distribution of KAP Scores*

Knowledge Score	18-25	26-40	41-60	Above 60	Total
Poor (0-3)	3	3	7	2	15(21.7%)
Average (4-6)	3	11	10	2	26(37.7%)
Good (7-9)	12	7	8	1	28(40.6%)
Mean Knowledge Score	6.67	5.8	5.36	4.8	
Attitude and Practices Score					
Poor (0-2)	10	12	11	1	34(49.3%)
Average (3-4)	6	6	9	2	23(33.3%)
Good (5-6)	2	3	5	2	12(17.4%)
Mean Attitude and Practices Score	2.16	2.19	3	4	

Mean knowledge score of the participants was 5.79±2.6, while mean attitude and practices score was found to be 2.61±1.9. In the knowledge section, 89.86% knew about diabetes, 24.64% knew that diabetes was a genetic/hereditary disease, 68.12% knew correctly about the risk factors of diabetes, 55.07% knew how to measure blood glucose, 57.97% were aware of the complications due to diabetes/ hyperglycemia. 63.77% of the participants knew the beneficial effects of regular exercise on diabetes. 69.57% had awareness about healthy dietary habits and their effects on diabetes and blood glucose. 50.72% knew the effect of sugar in diet on

diabetes. 49.28% also had knowledge about the effects of active and passive smoking on diabetes.

In the attitude section, 52% had control over their weight. 57.97% took meals at regular times. 40.58% exercised regularly.

In the practices section, 23% got their blood pressure regularly checked. 33.33% got their blood sugar regularly checked. 53.62% got their HbA1c regularly checked.

Table 2: KAP of Diabetics V Non-Diabetics

	Diabetics	Non-Diabetics
Knowledge Score		
Poor (0-3)	7 (31.8%)	8 (17%)
Average (4-6)	12 54.5%)	14 (29.8%)
Good (7-9)	3 (34.6%)	25 (53.2%)
Mean	4.86	6.23
Standard Deviation	2.21	2.63
Attitude and Practices Score		
Poor (0-3)	9 (40.9%)	25 (53.2%)
Average (4-6)	10 (45.5%)	13 (27.7%)
Good (7-9)	3 (13.6%)	9 (19.1%)
Mean	2.86	2.49
Standard Deviation	1.49	2.06

DISCUSSION

This study was conducted because the implementation of the necessary lifestyle modifications involving dietary changes, exercise and health practices are influenced by the knowledge, attitudes and practices of the individual, in addition to his or her values and cultural outlook. Similar studies establish a standard for recognizing diabetes knowledge levels, the current attitudes and practices and the factors that influence them. A KAP study of diabetic patients in the United Arab Emirates published in 2013 showed low levels of diabetes knowledge among patients in the UAE with 31% scoring in the “Poor" category. It is consistent with this study showing a “Poor" knowledge score among 31.8% of the diabetics.[9]

The study of 43 participants revealed very positive attitudes and medium levels of knowledge, and practice among diabetic patients attending the Carenage Health Centre.[10]

In this study, the level of knowledge was low in 21.7%, average in 37.6 % and good in 40.6 % of the participants. The attitude and practices scores were worse than previous studies with 49.3% of the respondents scoring in the poor category and 33.3% falling in average category. This is significantly worse than 75% scoring average and 14% scoring poor in a similar Bangladeshi study.[11]

In this study, 89.8% of the respondents had an idea about diabetes which is consistent with a Sri Lankan study showing 97% of the respondents having a familiarity with the disease.[12] 68.1% of the respondents knew about the risk factors for diabetes which is a good score compared to 42% in a Saudi Arabian study.[13] Younger age groups tend to be more informed about diabetes and score highly in all sections which is consistent with this study.[12] Generally, the knowledge scores were average to good which is consistent with previous studies.

It was observed that the presence of good knowledge scores did not translate into good attitude and practice scores. Despite understanding the risk factors of and precautions for diabetes, most patients did not make sufficient effort to minimize their risks.[12]

CONCLUSION

This study gives us a snapshot of the current status of knowledge, attitudes and practices related to the control of blood sugar level in the population of Faisalabad. The adequate knowledge about blood sugar control did not translate into proper and useful attitudes and practices even for those who scored well. Better knowledge among the younger respondents provides the solitary bright spot. This and similar studies should be used for national diabetes awareness campaigns. The modification of the approach and attitudes towards education on diabetes is the need of the hour.

Limitations of Study

The study is limited in its location and sample size and all the general biases are applicable. Larger scale studies of similar nature should be conducted before a firm final conclusion can be made about

knowledge, attitude, and practices pertaining to diabetes of the citizens of Faisalabad.

REFERENCES

1. About diabetes [Internet]. WHO. World Health Organization; 2013 [cited 2020Mar1]. Available from:https://web.archive.org/web/20140331094533/http://www.who.int/diabetes/action_online/basics/en/
2. Home [Internet]. International Diabetes Federation - Home. [cited 2020Mar1]. Available from: https://www.idf.org/aboutdiabetes/what-is-diabetes.html
3. Schnell O, Hanefeld M, Monnier L. Self-monitoring of blood glucose: a prerequisite for diabetes management in outcome trials. Journal of diabetes science and technology. 2014 May;8(3):609-14.
4. Shrivastava SR, Shrivastava PS, Ramasamy J. Role of self-care in management of diabetes mellitus. Journal of Diabetes & Metabolic Disorders. 2013 Dec; 12(1):14.
5. Bukhsh A, Khan TM, Nawaz MS, Ahmed HS, Chan KG, Lee LH, Goh BH. Association of diabetes-related self-care activities with glycemic control of patients with type 2 diabetes in Pakistan. Patient preference and adherence. 2018;12:2377.
6. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes care. 2004 May 1;27(5):1047-53.
7. Hamilton MT, Hamilton DG, Zderic TW. Sedentary behavior as a mediator of type 2 diabetes. In Diabetes and Physical Activity 2014 (Vol. 60, pp. 11-26). Karger Publishers.
8. Editor Posted on 15th January 2019, Editor. Fast food is undoubtedly very popular in the UK but is closely linked with health problems including obesity, type 2 diabetes and cardiovascular disease. [Internet]. Diabetes. 2020 [cited 2020Mar1]. Available from: https://www.diabetes.co.uk/food/fast-food-and-diabetes.html
9. Al-Maskari F, El-Sadig M, Al-Kaabi JM, Afandi B, Nagelkerke N, Yeatts KB. Knowledge, attitude and practices of diabetic patients in the United Arab Emirates. PloS one. 2013;8(1).
10. Beaubrun-Toby L. Knowledge, attitudes and practices of diabetics attending the Carenage Health Centre, in St. George West, Trinidad.
11. Mumu SJ, Saleh F, Ara F, Haque MR, Ali L. Awareness regarding risk factors of type 2 diabetes among individuals attending a tertiary-care hospital in Bangladesh: a cross-sectional study. BMC research notes. 2014 Dec 1;7(1):599.
12. Herath HM, Weerasinghe NP, Dias H, Weerarathna TP. Knowledge, attitude and practice related to diabetes mellitus among the general public in Galle district in Southern Sri Lanka: a pilot study. BMC public health. 2017 Dec 1;17(1):535.
13. Aljoudi AS, Taha AZ. Knowledge of diabetes risk factors and preventive measures among attendees of a primary care center in eastern Saudi Arabia. Annals of Saudi medicine. 2009 Jan;29(1):15-9.

BURDEN OF ANXIETY AND ITS ASSOCIATED FACTORS DURING THE TIME OF COVID-19 PANDEMIC

Fatima Sakhawat,[1] Faiza Sakhawat,[2] Muhammad Arslan,[3] Huda Abbas[4]

How to cite: Sakhawat F, Sakhawat F, Arslan M, Abbas H. Burden of anxiety and its associated factors during the time of COVID-19 pandemic. JAIMC. 2021; 19(1): 40-45.

Abstract

Background: A highly medically and psychologically devastating situation has been developed across the globe with the emergence of novel corona virus pandemic. Countrywide lockdown, quarantine and social distancing protocols have resulted in psychological trauma and devastating effect on mental health of general population

Objectives: To estimate the burden of anxiety and its associated factors in our population.

Methodology: A cross sectional study was done and data was collected through Google forms. Snowball type of sampling was used .The questionnaire included demographics, impact of pandemic on lives of people and 7-GAD scale. 7-GAD scale was used to categorize the anxiety levels in people from minimal to severe. Responses were collected from June 14, 2020 to June 18, 2020 and a total of 473 forms were included in the study. Data analysis was done by using SPSS version 24. Descriptive analysis, cross tabulation and Pearson's chi square test were applied. P value of < 0.05 was considered statistically significant.

Results: About 8.1% of the respondents had been affected by COVID-19 and 62.4% people had their relative or friend affected by COVID-19 infection. 35.7% people are suffering from moderate to severe anxiety. Gender, occupation, effect on family income, COVID-19 infection of the respondent himself or other family member/friend, increased screen time and reduced physical activity are all predictors of development of anxiety in our population.

Conclusion: Considering the results showing higher incidence of moderate to severe anxiety among people, immediate measures should be taken to address the situation and to make strategies to support their mental health.

Key Words: COVID-19, pandemic, 7-GAD scale, psychological impact, economic impact, predictors of anxiety

China was the first country when it comes to the emergence of COVID-19. Initially, it was declared as Public Health Emergency of International Concern by WHO. In a blink of eye, the virus had spread to various parts of the world. So, it was then declared as a pandemic.[1] It was highly devastating medically as well as psychologically as we were unprepared to cope up with the situation. This epidemic initially led to country wide lockdown which lasted for about 2 months. The continuous threat of spread of the virus demanded adaption to social isolation, closure of workplaces and businesses. School and universities are still closed. This has already caused high degree of psychological trauma to the people across country, in addition to the physical ailment. So, coming up with the studies to find out the direct and indirect effects of this pande-mic on human minds was the need of hour so that it can measure the impact it has created on people and how to protect their mental health from deteriora-tion. Researches from previous historical pandemics showed that the quarantine, fear of getting infection, fear of loss of loved ones, loss of

1. Fatima Sakhawat
2. Faiza Sakhawat
3. Muhammad Arslan
4. Huda Abbas

1. *Allama Iqbal Medical College, Lahore*
2. *Community Medicine Department, Quaid e Azam Medical College, Bahawalpur*

Correspondence:
Dr. Fatima Sakhawat, *Allama Iqbal Medical College, Lahore, Email: fatimasakhawat1@gmail.com*

Submission Date: 21-10-2020
1st Revision Date: 28-11-2020
Acceptance Date: 10-12-2020

complete freedom, inability to figure out the consequences, feeling of things slipping out of hands, inadequacy of food and other basic necessities of life and economy crises led to development of anxiety disorders in the populations. And those anxiety disorders did last even after the end of pandemic for considerably long periods of time.[2] According to a research conducted in China, 53.8% suffered from moderate to severe psychological effects due to this pandemic, 16.5% suffered from severe depressive symptoms, 28.8% suffered from moderate to severe anxiety levels and 8.1% suffered from moderate to severe stress.[3] Generalized Anxiety Disorder 7-item scale is widely used by health care professionals in the world. It saves time and is well known for the convenience of usage and reliability in making diagnosis. It helps in measurement of severity of diagnosis.[4] It also helps in screening of social anxiety, panic and post-traumatic stress disorder.[5]

COVID-19 pandemic itself is already a huge burden on feeble health care system of Pakistan. under such circumstances, psychological ailments will further incapacitate it leading to the point where it can even be paralyzed.[6] Despite of its due importance, insufficient research is done on this topic in our country when it comes to the aspect of literature review. We need studies to understand emotions of the population and factors affecting their mental peace under such circumstances. Campaigns on awareness of importance of mental health are the need of hour to keep people mentally fit.[7]

METHODOLOGY

It is cross sectional type of study .We calculated sample size using Open Epi software at 95% confidence interval and taking margin of error equal to 5%.Frequency of the anticipated factor was taken equal to 35.1%. The sample size calculated by software was 350. An online form was created via Google forms A total of 473 forms were collected and included in the study. Snowball type of sampling was done. Questions related to demographics and impact of pandemic on lives of people were asked. The online questionnaire also included questions from 7-GAD scale. 7-GAD scale is used to categorize the anxiety levels in people from minimal to severe. It includes 7 questions related to basic anxiety symptoms and the frequency with which they affect life of the person. The questionnaire was shared via WhatsApp and other social media to the contacts of researchers. Informed consent for the use of data for research purposes was taken. Responses were collected from June 14, 2020 to June 18, 2020. Data analysis was done by using SPSS version 24. Descriptive analysis was done. Cross tabulation was done between degree of anxiety and various demographic and personal factors. Peasrson's chi square test was applied to find out the statistical significance. P value of < 0.05 was considered statistically significant.

RESULTS

Out of 473 people, 72.9% were female and 27.1% were male. About 87.9% people belonged to age group of 21-30 years. 91.1% people belonged to urban area while 8.9% people belonged to rural areas. 71.5% were students, 11% were government employees, 8.7% were doing private jobs, 5.5% were unemployed, 2.1% were housewives, and 1.3% people had their own business.

41.9% people had their family income affected due to corona pandemic.62.4% people had their relative or friend affected by COVID-19 infection. Considering the infection in respondents' family and friends, 33% of the patients recovered, 22.6% patients were still under treatment, 6.8 % patients passed away while family and friends of 37.6% of respondents were not affected till then. In this study about 8.1% of the respondents had also been affected by COVID-19 infection. 92.8% of the respondents lived with their families during the pandemic. 87.3% people were used to discuss their life problems with others when needed .Screen time was increased than that of usual in 90.3% of people in study. Moreover, the lockdown due to pandemic led to reduced

physical activity in 81.3% people.79.3% of the people strictly observed the lockdown.

Incidence of moderate to severe anxiety is 40% among the female population in this study. We found that Female gender is more prone to development of anxiety (p=0.00). 41.6% of people who have their family income affected due to ongoing pandemic are suffering from moderate to severe grades of anxiety hence, more anxiety is seen in individuals whose family income is affected by the pandemic (p=0.005) and among those who either themselves or have any family members, friends affected by COVID-19 (p=0.007,0.048 respectively).Incidence of moderate to severe anxiety among people who had their relatives affected by corona infection is 60% while it is 47.3% among individuals who themselves are affected by the corona infection. Similarly, higher incidence of moderate to severe anxiety is seen among those individuals who had their relative passed away due to corona infection (46.9% of people with their relative passed away) and those whose relative is still under treatment (48.6% of people with their relative under treatment)(p=0.008). Higher incidence of moderate to severe anxiety is also seen among housewives (66.7% of the all housewives in the sample), students (37.3% of all students) and government employees (30.8% of all government employees), so the occupation also acts a predictor of anxiety amidst corona pandemic (p=0.077).50% of the people who did not discuss

Table 1:

	Levels of Anxiety			
	Minimal Anxiety	**Mild Anxiety**	**Moderate Anxiety**	**Severe Anxiety**
GAD-7 score	0-4	5-9	10-14	15-21
Frequency	126	178	98	71
Percentage	26.6%	37.6%	20.7%	15%

Table 2:

		Grade of Anxiety				P-Value
		Minimal anxiety	**Mild anxiety**	**Moderate anxiety**	**Severe anxiety**	
Gender	Male	53	44	16	15	0.000
	Female	73	134	82	56	
Occupation	Government job	14	22	9	7	0.077
	Private job	17	16	5	3	
	Business	2	4	0	1	
	Student	82	130	70	56	
	Housewife	2	1	5	1	
	Unemployed	9	5	9	3	
Family income affected by pandemic	Yes	37	78	44	38	0.005
	No	89	100	54	33	
Any friend or family member affected by COVID-19 Infection.	Yes	67	112	65	51	0.048
	No	59	66	33	20	
Outcome of COVID-19 infection in friends or family member of participant	Patient recovered	38	69	31	18	0.008
	Patient passed away	9	8	6	9	
	Patient is still under treatment	20	35	28	24	
	No family member or friend affected till now	59	66	33	20	
Participant affected by COVID-19 infection	Yes	1	19	11	7	0.007
	No	124	159	86	64	
Participant discusses problems when needed	Yes	114	160	84	55	0.034
	No	12	18	14	16	
Screen time increased than before during lockdown period	Yes	108	167	86	66	0.078
	No	18	11	12	5	
Effect of lockdown on routine physical activity	Increased than before	36	25	14	11	0.006
	Decreased than before	90	153	84	60	

their problems with others suffered from moderate to severe anxiety in this study. Less anxiety is seen among those participants who discussed their problems with friends and family when needed with the incidence of moderate to severe anxiety equal to 33.6 % among them (p=0.034). More anxiety is seen among those who had increased screen times (p=0.078) . Incidence of moderate to severe anxiety among them is found to be 59.2%. Similarly, decreased physical activity during the pandemic phase is also a predictor of increased anxiety among people (p=0.006).Incidence of moderate to severe anxiety among those who had reduced physical activity during pandemic times is 37.2%. (Table 2)

DISCUSSION

Epidemics and pandemics drastically affect mental health of the population. They have a great influence on thoughts and behavior of people and can ultimately end up in development of various psychiatric ailments among people, the most common of which is anxiety.[8] We are facing similar cicrumstances and people are living their lives in the way the never imagined ever before. Social distancing and interpersonal isolation have become very essential part of our lives now. Living lives in such an era of uncertainity when it comes to health and well-being, can make a person stressed and depressed. Such ailments have drastic outcomes in a long run. Looking into the history, we can see that suicide rates increased dramatically after the outbreak of Spanish flu in 1918.[9] Therefore, there is a need to make timely strategies to support people emotionally in such difficult times and to prevent such drastic outcomes. The goal of the study was to determine anxiety levels in our population due to COVID-19 pandemic by using GAD-7 scale.GAD-7 scale is widely known in clinical practice of psychiatry. It is known for its convenience in the use as the scale comprises of 7 simple questions which make the process of diagnosis easier for both patient and doctor. It is a valid tool to assess Generalized Anxiety Disorder and its severity among people and is widely used in outpatient and research practices.[10]

According to this study, 15% people were suffering from severe anxiety while 20.7% people were suffering from moderate anxiety. This result is comparable to a study in china where 28.8% people reported with moderate to severe anxiety patterns.[11] A sudden event of epidemic or pandemic due to newly emerged microorganism brings a lot of negativity, stress and anxiety with it.[12] This study reported that female gender is more prone towards development of anxiety. A meta-analysis shows similar results that female are more prone to development of anxiety and depression than that of male.[13] Previous mental or psychiatric ailments and physical ailments also make a person prone to develop anxiety and depression during such hard times.[14]

Higher incidence of severe anxiety is seen among students, government employees and businessmen. This might be due to fear of uncertainties of the future, negative impact of pandemic on educational and economical system, risks of financial instability ,inability to enjoy the efficient learning as they used to do before the pandemic.[15]

Negative impact of this pandemic on family income led to stimulate anxiety among people. Economic instability and inability to make both ends meet leads to mental frustration and is a predictor of development of psychologic ailments among people. Some people have totally lost the source of their daily income. Such experiences drastically affect mental health of not only a single person but of all members of family who collectively suffer its consequences. Lockdowns, isolation and quarantine harmfully impact the economic situation of low income people and daily wagers, this in a long term badly affects their mental well-being.[16]

More anxiety levels are seen in individuals who either themselves are suffering from COVID-19 infection or have any family member/friend affected by the virus. It may be because of fear of losing the dear ones. Similarly, more anxiety is seen among individuals who had their relative passed away due to covid-19 infection and those who still have their

relative under the treatment process. Significant anxiety among people may be due to unpredictability of the situation, fear of being lonely and helpless.[17] At such point, the proven contagiousness of novel corona virus may also be the factor promoting anxiety among the individuals.[18] In this time of medical emergency, psychological interventions must be added into treatment plans to overcome the state of anxiety and depression associated.

Interpersonal communication is seen as a protective factor under such circumstances. Trends of anxiety get less prominent when it comes to discussion of problems with friends and family. It acts as a tool for mental peace towards various draining life situations. It acts as a source of emotional support under times of distress and crises.

A lot of modifications in lifestyle of people are observed in pandemic days. People are used to spend longer times watching television, busy with their phones and laptops. Such habits make people prone to develop anxiety. Exposure to mass media plays a vital role in determining this factor. While viewing exaggerated and sensational headlines, hopelessness and helplessness a person feels can make him feel more anxious. It leads to a state where person begins to distrust the actions by higher authorities and tries to avoid medical consultation when he feels diseased.[19]

Reduced physical activity was also one of negative impacts which the pandemic created on individual lives. This may also be the cause of increased levels of anxiety in people. How both factors are actually related to each other is poorly understood but according to a research certain adaptations in Hypothalamic pituitary axis, Autonomic nervous system and immune complex of the body help in reducing stress in response to increased physical exercise.[20]

There are some limitations in our study as well. Firstly the questionnaire was in English and not all people in our country understand and respond to English language well. Secondly, social media was used to send the questionnaire due to restricted outdoor activity amidst pandemic. So, this questionnaire could not have reached the people who don't use social media platforms. Moreover, this study should be conducted at larger scale to include above mentioned groups as well so that we can have more generalized results.

CONCLUSION

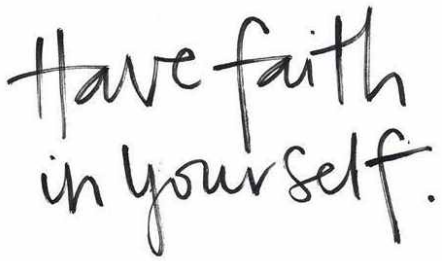
35.7% people are suffering from moderate to severe anxiety. Gender, occupation, effect on Family income, COVID-19 infection of the respondent himself or other family member/friend, increased screen time and reduced physical activity are all predictors of development of anxiety in our population. These results clearly show that such situation is needed to be addressed on urgent basis to support mental health of people. Help of social and mass media can be taken in this regard. It is important that people should be made to learn stress relieving exercises and techniques so that they can help themselves. Nationwide support by government and people should be given to the ones with low income and daily wagers. Provision of social support is mandatory to help people realize that we all are in the same boat. Along with medical treatment of people, support by a psychiatrist or psychologist should also be made mandatory in hospitals.

REFERENCES

1. WHO rolling updates on coronavirus disease (COVID-19) (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen)
2. Brooks, S.K.; Webster, R.K.; Smith, L.E.; Woodland, L.; Wessely, S.; Greenberg, N.; Rubin, G.J. The psychological impact of quarantine and how to reduce it: Rapid review of the evidence. Lancet 2020;395:912–920
3. Cuiyan W, Riyu P , Xiaoyang W, Yilin T, Linkang X , Cyrus S. and Roger C. Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China. international journal of environmental research and public health ;17(5)
4. S.U. Johnson, P.G. Ulvenes, T. Øktedalen. Psychometric properties of the general anxiety disorder 7-

Item (GAD-7) scale in a heterogeneous psychiatric sample.Frontiers in psychology (2019), p. 1713(2)

5. E. Moreno, R. Muñoz-Navarro, L.A. Medrano, C. González-Blanch, P. Ruiz-Rodríguez, J.T. Limonero, L.S. Moretti, A. Cano-Vindel, J.A. Moriana. Factorial invariance of a computerized version of the GAD-7 across various demographic groups and over time in primary care patients. J. Affect Disord, (2019), pp. 114-121
6. Hashmi AM, Saleem HA. New Horizons: COVID-19 and the Burden of Neuropsychiatric Illness in Pakistan. Pak J Med Sci. 2020; 36(COVID19-S4), pp95-98
7. Wenjun Cao, Ziwei Fang, Guoqiang Hou, Mei Han, Xinrong Xu, Jiaxin Dong, Jianzhong Zheng, The psychological impact of the COVID-19 epidemic on college students in China. Psychiatry Research 2020; 287.
8. S.L. Mei, J.X. Yu, B.W. He, J.Y. Li.Psychological investigation of university students in a university in Jilin province .Med Soc (Berkeley), 2011;24 (05): 84-86.
9. Wasserman IM. The impact of epidemic, war, prohibition and media on suicide: United States, 1910–1920. Suicide Life-Threat Behavior. 1992; 22:240–254.
10. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. Arch Intern Med. 2006;166(10):1092–1097
11. Cuiyan W, Riyu P , Xiaoyang W, Yilin T, Linkang X , Cyrus S. and Roger C. Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China. international journal of environmental research and public health ;17(5)
12. Huang Y, Zhao N. Generalized anxiety disorder, depressive symptoms and sleep quality during COVID-19 outbreak in China: a web-based cross-sectional survey. Psychiatry research, 2020;288
13. Lim, G.Y. Prevalence of Depression in the Community from 30 Countries between 1994 and 2014. Sci. Rep. 2018, 8, 2861
14. Cacioppo, J. T., Hughes, M. E., Waite, L. J., Hawkley, L. C., & Thisted, R. A. .Loneliness as a specific risk factor for depressive symptoms: Cross-sectional and longitudinal analyses. Psychology and Agin ,2006; 21(1), 140–151
15. C. Wang, P.W. Horby, F.G. Hayden, G.F. Gao A novel coronavirus outbreak of global health concern Lancet 2020; 395 (10223) : 470-473.
16. Margaret Douglas, Srinivasa Vittal Katikireddi. Mitigating the wider health effects of covid-19 pandemic response BMJ 2020;369: 1557.
17. A Zandifar, R Badrfam. Iranian mental health during the COVID-19 epidemic; Asian journal of psychiatry ,2020;51
18. Z. Song, Y. Xu, L. Bao, L. Zhang, P. Yu, Y. Qu, H. Zhu, W. Zhao, Y. Han, C. Qin. From SARS to MERS, Thrusting Coronaviruses into the spotlight .Viruses 2019;11 (1) :p. 59
19. Ravi Philip Rajkumar. COVID-19 and mental health: A review of the existing literature. Asian Journal of Psychiatry 2020;52
20. Hamer M., Endrighi R., Poole L. (2012) Physical Activity, Stress Reduction, and Mood: Insight into Immunological Mechanisms. In: Yan Q. (eds) Psychoneuroimmunology. Methods in Molecular Biology (Methods and Protocols) 2020; 934:89-102



FREQUENCY OF COLUMNAR CELL LESIONS OF BREAST AND ASSOCIATION WITH MALIGNANCY

Maham Akhlaq,[1] Rabia Altaf,[2] Safeena Sarfraz,[3] Saeed Ahmad[4]

How to cite: Akhlaq M, Altaf R, Sarfraz S, Ahmad S. Frequency of columnar cell lesions of breast and association with malignancy. JAIMC. 2021; 19(1): 46-49.

Abstract

Background: Histologically and recently with advances in medical genetics it is suggested that Columnar cell lesions (CCL) of breast may play a role in low grade breast carcinoma pathway. However there is still some conflicting data regarding its association with malignancy. And its role as precursor of malignancy is still poorly understood.

Methodology: Sixty consecutive breast biopsies, both benign and malignant were collected at the department of Pathology, King Edward medical college, Lahore. They were evaluated for CCL and final diagnosis of benign and malignant was made.

Results: Out of the 60 consecutive samples 44(73.3%) were benign and 16(26.7%) were malignant. CCL was seen in (41.7%) of total cases. CCL were encountered more frequently in benign breast disease (43%). Columnar cell hyperplasia (CCH) (23.3%) was the commonest finding, followed by columnar cell change (CCC) (16.7%) and Flat epithelial atypia (FEA) (1.7%). However no association was seen between CCL and breast carcinoma.

Conclusion: CCL are frequently encountered in our setup .Of all the CCL, CCH is the commonest and FEA is the least common. There was no association of CCL with malignancy seen (p=>0.05).

KeyWords: Columnar cell lesions (CCL), Columnar cell hyperplasia (CCH), Flat epithelial atypia (FEA), Breast biopsy, Breast malignancy.

Columnar cell lesions are characterized by replacement of cuboidal epithelium of the terminal duct lobular unit (TDLU) of breast with tall columnar cells. Due to their association with micro calcifications they have been increasingly picked up on routine mammography evaluation.[1]

Columnar cells lesions are classified into 3 categories; columnar cell change (CCC), columnar cell hyperplasia (CCH) and Flat epithelial atypia (FEA). CCC is the simplest form characterized by dilation of TDLU lined by tall columnar cells showing apical cytoplasmic blebs with oval bland nuclei perpendicular to the basement membrane. CCH is identified when the same dilated TDLU is lined by more than 2 cell layer of columnar epithelium having similar characteristics as of CCC. In case atypia is encountered in such lesions these are labeled as FEA. Which are recognized more and more due to their association with microcalcifications. However there is marked interobserver variability in identifying these lesions.[2,3] On immunostaining these lesions are reactive for broad spectrum keratin cocktails, but are negative for High molecular weight keratins like CK 5/6 which distinguishes them from usual ductal hyperplasia. In addition they are strongly positive for ER and PR and Ki-67 index is higher in FEA[3] however they are negative for p53.[4]

These lesions have been labelled as precursors for low grade invasive carcinomas. Data from various studies reveal that core biopsies of the

1. Maham Akhlaq 2. Rabia Altaf
3. Safeena Sarfraz 4. Saeed Ahmad
1. *Assistant Professor Pathology, University of Health Sciences, Lahore*
2-3: *Demonstrator Pathology, King Edward Medical University, Lahore.*
4. *Professor of Pathology, King Edward Medical University, Lahore.*

Correspondence:
Dr. Maham Akhlaq, Assistant Professor Pathology, *University of Health Sciences, Lahore,* Email : maham.inaam@hotmail.com

Submission Date: 11-10-2020
1st Revision Date: 25-11-2020
Acceptance Date: 30-11-2020

atypical lesion frequently are upgraded to malignant lesions on subsequent excisional biopsies[5] and FEA share histopathological features and immunohistochemical profile with low grade invasive carcinoma and ductal carcinoma insitu.as well as tubular carcinoma.[6] These diseases are generally not reported and overlooked in our setup. Due to their association with the premalignant and malignant diseases, their reporting, clinical follow up or subsequent biopsy is important. These patients should be followed up more promptly for better patient outcome and survival.[7]

In this study the frequency of CCL in breast biopsy specimen in King Edward Medical University will be calculated and significance of CCL and FEA in benign and malignant pathologies will be established. With this study we aim to look at the progression of CCLs and FEA to malignancy.

METHODOLOGY

Study Design:

Descriptive, Cross sectional Survey

Setting:

Department of Histopathology, King Edward Medical University, Lahore

Sample Size:

Sample size of 60 cases is calculated with 95% confidence level, 12.5% margin of error and taking patients expected percentage that is 37% that show presence of columnar cell lesions in breast lumps (core needle and excisional biopsies).

Sampling Technique

Non probability, consecutive sampling.

Statistical Analysis:

Pearson Chi square was applied to calculate significance.

RESULTS

In our study we catered to all age groups starting from 15 upto 60 years of age In our setup we observed that most frequent age bracket for a breast biopsy was from 20 to 30years (41%) followed by even younger group of teens 15-20 years (17,9%).

In this study we looked at 60 breast biopsy samples. Out of the 60 consecutive samples 44(73.3 %) were benign and 16(26.7%) were malignant. The most frequent diagnosis was fibroadenoma (36.1%) followed by ductal carcinoma (26.2%). The rest were benign fibroepithelial lesions including fibrocystic change and papillomatosis.

The most common columnar cell lesion encountered was CCH (figure1) at 23.3% followed by CCC (figure 2) at 16.7% and least common was FEA (figure 3) at 1.7% in the total of breast biopsies reviewed in this study n=60. These include both benign and malignant cases.

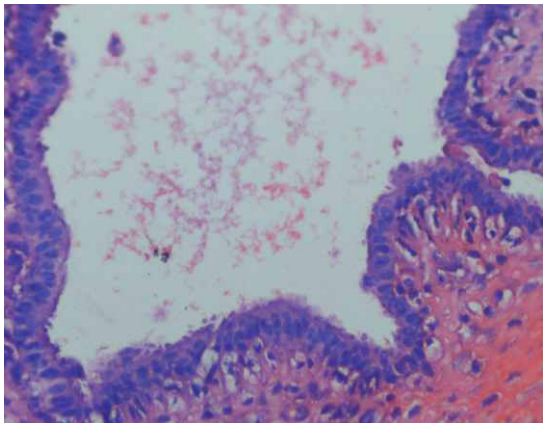


Figure 1: *Columnar Cell Change at 200x Magnification.*

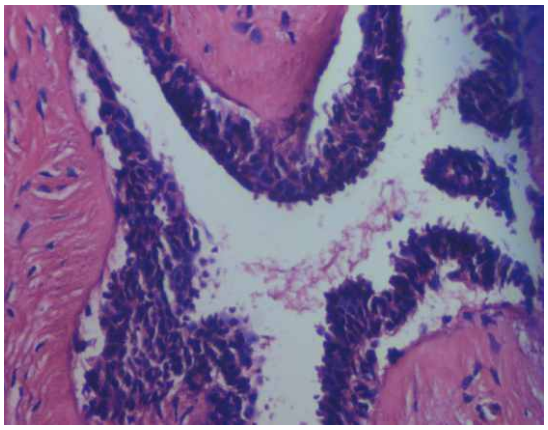


Figure 2: *Columnar Cell Hyperplasia at 100x Magnification*

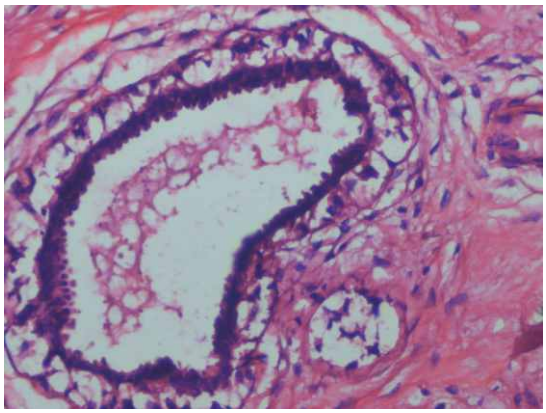


Figure 3: *Flat Epithelial Atypia at 200x Magnification*

The columnar cell lesion most commonly encountered in a malignant breast biopsy was CCH at 25% (Table1). CCC was seen in 6.25% cases where as no FEA was noted in malignant breast biopsy. There was no significant association seen.

Table 1: *Presence of Columnar Cell Lesion in Benign and Malignant Breast Biopsy*

Columnar cell lesion present	Diagnosis of Biopsy		P value
	Benign (n=44) n(%)	Malignant (n=16) n(%)	
Columnar cell change	9(20.4%)	1(6.25%)	>0.05 (0.263)
Columnar cell hyperplasia	10(22.7%)	4(25%)	>0.05 (1.000)
Flat epithelial atypia	1(2.27%)	0 (0%)	>0.05(1.000)

P value calculated by Pearson Chi square
P value <0.05 considered significant

DISCUSSION

Columnar cell lesions have been of great interest for pathologist as they have been linked frequently to microcalcifications on mamography.[3,8] These lesions have been linked in previous studies to atypical hyperplasia, lobular and ductal carcinoma.[9] However its position as a precursor to malignancy still remains controversial to this day.

Earlier studies done on these lesions have shown a link to tubular carcinoma. But this study by Abdel-Fateh et al. looked only at tubular carcinomas and not the full spectrum of breast diseases including benign and other malignancies.[10] A study conducted in Netherlands showed atypical CCC with ductal carcinoma insitu (DCIS) and invasive breast carcinoma (IDC) ductal type but also noted that presence of atypical ductal hyperplasia in CCL (ADH-CCL) has similar outcome. This study concluded that presence of CCL and ADH-CCL in core needle biopsy requires an excisional biopsy.[11] Boulos et al also conducted a similar study and concluded that the risk of breast malignancy does not significantly increase with finding of CCL however it may warrant a closer look for ADH as that can be worrisome in a benign breast biopsy.[12]

Despite the compelling findings a relatively recent study of 2018 studying long term follow up of 70 cases of FEA shows no significant risk of subsequent malignant disease.[13] A similar study with a large cohort (1751 core biopsies with 63 FEA) also concluded the same.[14] Another study also suggests similar findings that CCL on their own are not significant risk for breast cancer independent of ADH.[15] But they do warrant a closer follow up.

CCLs are not routinely documented in breast biopsies in our setup and there is no data available on CCL in Pakistan, so we decided to look for these lesions in our population demographic and try to find a link of these lesions to malignancy. In our study we looked at 60 consecutive breast biopsies core needle and excisional. CCL were observed in 41.7% of the cases (both benign and malignant). Most of these patients were in the young demographic 20-30 years presenting mostly with benign breast pathologies. There was no significant link of CCL seen with malignancy (p>0.050). FEA was the least common pathology encountered and mostly CCH was seen on the edges of the malignant cases similar to the findings of Aroner etal.[15] Although our study does not show an association of CCH with malignancy but cases of malignancy were limited in number compared to the benign breast ones. However what was interesting was finding CCL especially CCC and CCH in quite a number of benign cases (19 out of 44) (43%) which leads to the perception that it's part of the benign spectrum rather than the premalignant or malignant one. More studies in our setup are required in a larger population with longer follow up in benign biopsies with CCL to establish this fact.

Our study will expectantly lead the way to further research in this field.

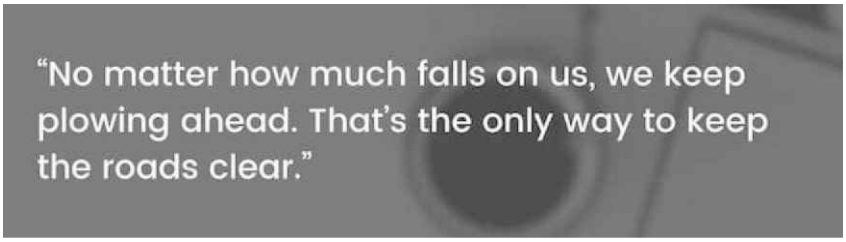
In this study we conclude that CCL are frequently seen in breast biopsies in our setup, However there is no significant association with malignancy.

Conflict of interest

No conflict of interest

REFERENCES

1. Schnitt SJ, Vincent-Salomon A. Columnar Cell Lesions of the Breast. Advances in Anatomic Pathology. 2003;10(3):113-24.
2. O'Malley FP, Mohsin SK, Badve S, Bose S, Collins LC, Ennis M, et al. Interobserver reproducibility in the diagnosis of flat epithelial atypia of the breast. Modern Pathology. 2006;19(2):172-9.
3. Logullo AF, Nimir C. Columnar cell lesions of the breast: a practical review for the pathologist. Surgical and Experimental Pathology. 2019;2(1):2.
4. Demiralay E, Demirhan B, Koçbiyik A, Sar A, Altaca G. Immunohistochemical and morphologic findings in columnar cell lesions of the breast. Indian Journal of Pathology and Microbiology. 2011;54(2):335-8.
5. Calhoun BC. Core Needle Biopsy of the Breast: An Evaluation of Contemporary Data. Surgical pathology clinics. 2018;11(1):1-16.
6. Collins LC. Precursor Lesions of the Low-Grade Breast Neoplasia Pathway. Surgical pathology clinics. 2018;11(1):177-97.
7. Acott A, Mancino A. Flat epithelial atypia on core needle biopsy, must we surgically excise? The American Journal of Surgery. 2016;212(6):1211-3.
8. Pandey S, Kornstein MJ, Shank W, Paredes ESd. Columnar Cell Lesions of the Breast: Mammographic Findings with Histopathologic Correlation. RadioGraphics. 2007;27(suppl_1):S79-S89.
9. Goldstein NS, O'Malley BA. Cancerization of small ectatic ducts of the breast by ductal carcinoma in situ cells with apocrine snouts: a lesion associated with tubular carcinoma. American journal of clinical pathology. 1997;107(5):561-6.
10. Abdel-Fatah TM, Powe DG, Hodi Z, Lee AH, Reis-Filho JS, Ellis IO. High frequency of coexistence of columnar cell lesions, lobular neoplasia, and low grade ductal carcinoma in situ with invasive tubular carcinoma and invasive lobular carcinoma. The American journal of surgical pathology. 2007; 31(3): 417-26.
11. Verschuur-Maes AHJ, Witkamp AJ, de Bruin PC, van der Wall E, van Diest PJ. Progression risk of columnar cell lesions of the breast diagnosed in core needle biopsies. International Journal of Cancer. 2011;129(11):2674-80.
12. Boulos FI, Dupont WD, Simpson JF, Schuyler PA, Sanders ME, Freudenthal ME, et al. Histologic associations and long-term cancer risk in columnar cell lesions of the breast: a retrospective cohort and a nested case-control study. Cancer. 2008; 113(9): 2415-21.
13. Ouldamer L, Poisson E, Arbion F, Bonneau C, Vildé A, Body G, et al. All pure flat atypical atypia lesions of the breast diagnosed using percutaneous vacuum-assisted breast biopsy do not need surgical excision. The Breast. 2018;40:4-9.
14. Martel M, Barron-Rodriguez P, Tolgay Ocal I, Dotto J, Tavassoli FA. Flat DIN 1 (flat epithelial atypia) on core needle biopsy: 63 cases identified retrospectively among 1,751 core biopsies performed over an 8-year period (1992-1999). Virchows Archiv : an international journal of pathology. 2007; 451(5): 883-91.
15. Aroner SA, Collins LC, Schnitt SJ, Connolly JL, Colditz GA, Tamimi RM. Columnar cell lesions and subsequent breast cancer risk: a nested case-control study. Breast Cancer Res. 2010;12(4):R61-R.



TRENDS OF ELASTOGRAPHIC CHANGES IN HEPATITIS C VIRUS PATIENTS AFTER ACHIEVING SUSTAINED VIRAL RESPONSE ON DUAL ANTIVIRAL THERAPY

Mujtaba Hasan Siddiqui,[1] Junaid Mushtaq,[2] Noor-ul-Arfeen,[3] Rizwan Elahi,[4] Khawar Abbas Chaudhry,[5] Muhammad Azhar Shah[6]

How to cite: Siddiqui MH, Mushtaq J, Arfeen N, Elahi R, Chaudhry KA, Shah MA. Trends of elastographic changes in hepatitis C virus patients after achieving sustained viral response on dual antiviral therapy. JAIMC.2021; 19(1): 50-55.

Abstract

Background: Hepatitis C is an infectious disease caused by the hepatitis C virus (HCV) that primarily affects the liver. The cause of hepatitis C, HCV, is a spherical, enveloped, single-stranded RNA virus belonging to the Flaviviridae family and Flavivirus genus. Serologic screening for HCV involves an enzyme immunoassay. Elastography is a medical imaging modality that maps the elastic properties and stiffness of soft tissue.

Objective: To find the frequency of serial elastography changes in hepatitis c virus patients after achieving sustained viral response on dual antiviral therapy

Methodology: This cross sectional study was conducted in the department of Medicine, division of Gastroenterology of Lahore general Hospital, Lahore from 1 June 2017 to 1 December 2018. Patients fulfilling the inclusion criteria went through elastography for the detection of elstographic changes. These patients were labeled as mild, moderate or severe fibrosis on the basis of elastrographic values. All the collected data was entered and analyzed on SPSS version 21.

Results: The mean age of patients was 37.40±12.69 years. Male to female ratio of the patients was 1.09:1. The mean duration of HCV was 4.40±2.93 months. No change was observed in 192 (50.77%) patients, mild to moderate changes were observed in 129 (33.08%) patients and severe change were seen in 63 (16.15%) patients.

Conclusion: The frequency of serial elastography is helpful in categorizing patients in mild, moderate and severe fibrosis in patients of hepatitis C, after achieving SVR on dual antiviral therapy.

Key Words: Elastography, HCV, sustained viral response, dual antiviral therapy

Hepatitis, refers to inflammation of the liver, may result from various causes, both infectious and noninfectious, which accounts for >50% of cases of acute hepatitis in US. Approximately 20% of patients with chronic hepatitis C eventually develop cirrhosis, as evidenced by the histologic changes of severe fibrosis and nodule formation.[1]

Antiviral medicines can cure approximately 90% of persons with hepatitis C infection, thereby reducing the risk of death from liver cancer and cirrhosis, but access of majority of these patients to the diagnosis and treatment is poor.[2] When treatment is necessary, the goal of hepatitis C treatment is cure. The standard of care for hepatitis C is changing rapidly. Until recently, hepatitis C treatment was based on therapy with interferon and ribavirin, which required weekly injections for 48 weeks. It cured approximately half of treated patients, but caused frequent and sometimes life-threatening adverse reactions.[3]

Several other newer direct acting antivirals

1. Mujtaba Hasan Siddiqui
2. Junaid Mushtaq
3. Noor-ul-Arfeen
4. Rizwan Elahi
5. Khawar Abbas Chaudhry
6. Muhammad Azhar Shah

1,3,6: Akhtar Saeed Medical & Dental College, Lahore
4. Gastroenterology Division, Lahore General Hospital, Lahore
5. Madina Munawwara, Saudi Arabia
6. Continental Medical College, Lahore

Correspondence:
Dr. Mujtaba Hasan Siddiqui
Associate Professor of Medicine, Akhtar Saeed Medical & Dental College, Lahore ; Email: omujidr@yahoo.com

Submission Date: 18-10-2020
1st Revision Date: 29-11-2020
Acceptance Date: 05-12-2020

have shown promise in clinical studies and are likely to be licensed soon. These agents seem to facilitate the use of shortened courses of combination interferon-free therapy, which are associated with high (>95%) SVR rates and relatively less toxicities.[4]

Transient elastography is an easy, non-invasive, reproducible technique that is well tolerated for staging non-significant fibrosis or severe fibrosis/ cirrhosis. The assessment of liver fibrosis using transient elastography may be useful to reduce the need for a liver biopsy.[5]

Non-invasive shear-wave elastography techniques to determine the fibrosis stage of the liver, such as transient elastography with fibroscan and acoustic radiation force impulse, have found their way into the standard diagnostics of chronic liver diseases.[6,7]

Shear-wave elastography techniques measure liver stiffness, which correlates well with histological stage of liver fibrosis.[8,9]

Liver cirrhosis represents a severe complication for hepatitis C patients. Patients with cirrhosis require immediate treatment; a SVR has been demonstrated to reduce the probability of complications and to improve the prognosis.[10] In patients with advanced fibrosis measured by transient elastography at the beginning of protease inhibitor-based therapy with SVR, liver stiffness was significantly reduced 24 weeks after treatment.[11]

Rationale of this study was to find the frequency of serial elastography changes in HCV patients after achieving SVR on dual antiviral therapy. Elastography can help in prediction of prognosis of HCV treatment and further course of the disease can be determined. There is no local evidence available in this regard and the extent of problem in local population is unknown. Prediction of the outcome of dual antiviral therapy in local population and to decide about the prognosis of patients remain unclear. That is why we want to conduct this study to find local evidence and implement the results of this study in future, which could help us in planning better management protocol for HCV patients. It was defined as patients who had HCV-RNA >15IU/ml in serum. Patients who had therapy with interferon plus sofosbuvir and sustained viral res-ponse (HCV-RNA<10IU/ml) would be achieved (on medical record). It was measured as values range from 2.5 to 75 kPA with values of <7.0 being normal and suggesting no or mild hepatic fibrosis, values of 7.1–13.7 suggesting moderate to advanced fibrosis and values of >13.8 suggesting cirrhosis.

METHODOLOGY

Using non-probability consecutive sampling, this cross sectional study included 390 patients with newly diagnosed HCV in outpatient department of gastroenterology, Lahore general Hospital, Lahore, between 1 June 2017 and 1 December 2018.

Patients of age 18-60 years, either gender with diagnosed HCV (on medical record) on dual antiviral therapy and achieved SVR (as per operational definition).

Those patients with comorbid conditions including hepatitis B virus, HIV or Hepatocellular carcinoma (medical record), those who had triple antiviral therapy (on medical record) and those with recurrent HCV (on medical record), were excluded from the study.

Written informed consent was taken. Basic demographics like name, age, gender, BMI and duration of HCV was noted. Then patients were undergone elastography for detection of elstographic changes. Patients were labeled as mild, moderate or severe cirrhosis on the basis of elastrography values (as per operational definition). All the data was recorded through a designed questionnaire.

Data was analyzed with IBM-SPSS version 21. Quantitative variables like age, BMI and duration of HCV were presented in Mean ±SD. Frequency and percentage was computed for qualitative variables like gender and elastrography changes (no, mild, moderate, severe). Effect modifiers like age, gender, BMI and duration of HCV was controlled through stratification. Post-stratification, chi-square test was applied with $p \leq 0.05$ taken as significant.

RESULTS

In this study, a total of 390 cases, with mean age of 37.40±12.69 years were enrolled with minimum and maximum ages of 17 & 60 years. There were 204 (52.3%) males and 186 (47.6%) females. Male to female ratio was 1.09:1. Mean BMI of the patients was 22.65±2.39 kg/m^2 with minimum and maximum values of 18.5 and 26.73. Mean duration of HCV of patients was 4.40±2.93 months. Mean scan value for the patients was 8.17±4.45, ranging from 2.5 to 17.9. No change on elastography was found in 198 (50.77 %) patients, mild to moderate change was observed in129 (33.08%) patients and severe change was observed in 63 (16.15%) patients (Fig 1).

The study results showed that, out of 234 patients with age ≤40 years, no change on elastography was found in 138 (58.9%) patients, mild to moderate changes were found in 51 cases (21.8%) and severe changes were found in 45 cases (19.2%). Similarly the patients with age > 40 years were 156 in which no change on elastography was found in 60 cases (38.4%), mild to moderate change was found in 78 cases (50%) and severe changes was seen in 18 cases (11.5%). Statistically significant difference was found between the elastography findings with age i.e., p-value=0.004 (Table 3).

In this study, the total number of male patients were 204 in which no change on elastography was found in 102 patients (50%), mild to moderate change was found in 75 cases (36.7%) and severe changes were observed in 9 cases (4.3%). Similarly the female patients were 186 in which no change on elastography was found in 96 cases (51.6%), mild to moderate changes were seen in 54 cases (29%) and severe changes were observed in 36 cases (19.3%). Statistically insignificant difference was found between the elastography findings with gender i.e. p-value=0.508 (Table 4)

The study results showed that patients with normal BMI were 309, in which no change on elastography was found in 144 (46.6%), mild to moderate changes were seen in 123(39.8%) and severe changes were observed in 42 patients (13.6%). Similarly, amongst 81 patients with abnormal BMI, no change on elastography was found in 54 (66.6%), mild to moderate changes were observed in 6 (25.9%) and severe changes were seen in 21 (25.9%). The data was not found to be statistically significant as far as BMI was concerned with a p-value of 0.631 (Table 5).

The results of this study showed that out of 252 patients with HCV duration of ≤5 months, no change on elastography was found in 120 patients (47.6%), mild to moderate changes were observed in 84 (33.3 %) and severe changes were seen in 48 cases (19%). Similarly, patients with HCV duration of > 5 months were 138 in which no change on elastography was found in 78 (56.5%), mild to moderate changes were found in 45 (32.6%) and severe change were observed in 15 (19.2%). This data of HCV duration was also not found to be significant statistically with a p-value of 0.428 (Table 6).

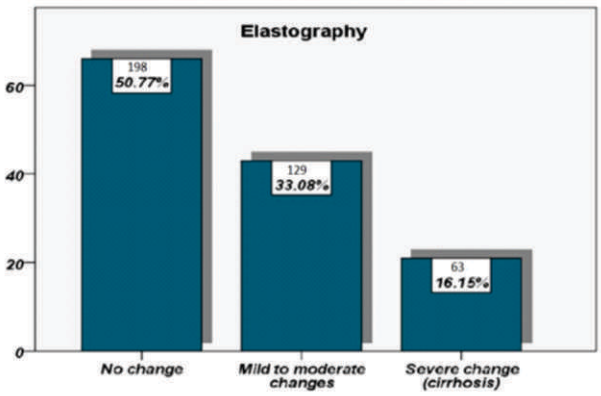


Fig 1: *Frequency Distribution of Elastography*

DISCUSSION

This present cross-sectional study was carried out at unit I, Department of Gastroenterology, Lahore general Hospital, Lahore to find the frequency of serial elastography changes in HCV patients after achieving SVR on dual antiviral therapy.

Table 1: *Descriptive Statistics of HCV Duration*

Duration Of HCV	N	390
	Mean	4.40
	SD	2.93
	Minimum	1
	Maximum	10

Table 2: Descriptive Statistics of Scan Values

Scan Values	N	390
	Mean	8.17
	SD	4.45
	Minimum	2.5
	Maximum	17.9

Table 3: Comparison of Elastography with Age

		Elastography change			Total
		No change	Mild to moderate	Severe (cirrhosis)	
Age (years)	⩽ 40	138	51	45	234
	> 40	60	78	18	156
Total		198	129	63	390

Chi value = 11.23 p-value=0.004*

Table 4: Comparison of Gender with Elastography

		Elastography change			Total
		No change	Mild to moderate	Severe (cirrhosis)	
Gender	Male	102	75	27	68
	Female	96	54	36	62
Total		198	129	63	390

Chi value = 1.35 p-value=0.508 NS

Table 5: Comparison of BMI with Elastography

		Elastography change			Total
		No change	Mild to moderate	Severe (cirrhosis)	
BMI	Normal	144	123	42	309
	Abnormal	54	6	21	81
Total		198	129	63	390

p-value=0.631 NS

Table 6: Comparison of Duration of HCV with Elastography

		Elastography change			Total
		No change	Mild to moderate	Severe (cirrhosis)	
Duration of HCV	⩽5	120	84	48	252
	>5	78	45	15	138
Total		198	129	63	390

Chi value=1.69 p-value=0.428 NS

HCV is a blood-borne hepatotrophic RNA virus of significant worldwide public health concern. Currently, there are 270–300 million people infected worldwide, with the incidence of HCV expecting to peak in the coming 10–20 years. Treatment of HCV aims to improve outcome by slowing or halting progression to cirrhosis and hepatocellular carcinoma. Serial liver biopsy during or following treatment is not considered necessary or ethical at present. Non-invasive methods of assessing pathological changes in the liver are being assessed. These are often expensive, conceptually difficult or require special equipment.[13,14] Elastography has been recommended to assess the damage to the liver by HCV and liver stiffness which correlates with the histological stage of liver fibrosis.[8,9]

In our study, no change on elastography was found in 198 (50.7%) patients, mild to moderate changes were observed in 129 (33%) and severe changes were seen in 63 (16.1%) patients. The data available to assess liver fibrosis by elastography is very limited and more studies are required to assess its role.

One study showed that transient elastography was attempted successfully in 69 patients at follow-up after HCV treatment with dual antiviral therapy. In this group, 59% had stiffness scores of <7.0 kPA (considered normal), 32% had values between 7.1 and 13.8 (suggestive of moderate to advanced fibrosis), and 9% had values above 13.8 kPA (suggestive of cirrhosis).[12]

A study by Gregory D. Kirk et al showed that elastography was extremely well accepted and tolerated. A total of 198 patients were offered the procedure and all complied. Valid results were obtained for 192 (97%) of these patients. The median liver stiffness measurement was 8.85 kPa (range, 3–75 kPa; IQR, 6.13–14.0 kPa). In linear regression models, Metavir fibrosis score was very strongly associated with liver stiffness measurement (P < .001), as were laboratory (AST level, ALT level, platelet count, AST-to-platelet ratio index, and albumin level) and histologic (steatosis and inflammation score) markers of liver disease.[15]

In patients with advanced fibrosis measured by transient elastography at the beginning of protease inhibitor-based therapy, who achieved SVR later, liver stiffness was significantly reduced 24 weeks

after treatment.[11]

A study by Vergara S recommended that the transient elastometry is quite accurate for detecting significant liver fibrosis and cirrhosis in HCV mono-infected patients. To diagnose significant liver fibrosis, a cutoff value of 7.2 kPa was associated with a positive predictive value of 88% and a negative predictive value of 75%. Thirty-four patients (20%) were misclassified when this cutoff value was used. Thirteen (24%) out of 54 patients with liver stiffness values <7.2 kPa had significant liver fibrosis detected by liver biopsy. To diagnose cirrhosis, a cutoff value of 14.6 kPa was associated with a positive predictive value of 86% and a negative predictive value of 94%.[16]

In a meta-analysis, Talwalkar et al found that transient elastography has a 91% specificity and an 87% sensitivity for detecting cirrhosis as compared to liver biopsy.[11]

One study by An Tang et al revealed that the technical and instrument-related factors and biologic and patient-related factors may constitute potential confounders of stiffness measurements for assessment of liver fibrosis. Future developments may expand the scope of elastography for monitoring liver fibrosis and predict complications of chronic liver disease.[17]

CONCLUSION

Our study showed that the frequency of serial elastography showed mild to moderate changes in fibrosis in almost 33% patients and severe change of fibrosis (cirrhosis) in 16% in HCV patients after achieving SVR on dual antiviral therapy. Transient elastography is a unique and non-invasive imaging modality to have a high accuracy for detecting mild to moderate fibrosis. It has excellent ability to assess the level of cirrhosis by a non-invasive method. The results of our study are in conjunction with the few studies already done in this regard. More studies and data is needed for further evaluation of the efficacy of this technique in the assessment of fibrosis in patients with HCV.

Acknowledgment

We are thankful to Dr. Rizwan Elahi for his efforts in compiling the data and reviewing the literature for this study.

REFERENCES

1. AM. B. Viral Hepatitis. 2014 [cited 2016]; Available from: http://emedicine.medscape.com/article/775507-overview#a2.
2. Organization. WH. Hepatitis C. . 2016 [cited 2016]; Available from: http://www.who.int/ mediacentre/factsheets/fs164/en/.
3. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 2012; 380 (9859):2095-128.
4. Feeney ER, Chung RT. Antiviral treatment of hepatitis C. Bmj 2014;349:g3308.
5. Stasi C, Piluso A, Arena U, Salomoni E, Montalto P, Monti M, et al. Evaluation of the prognostic value of liver stiffness in patients with hepatitis C virus treated with triple or dual antiviral therapy: A prospective pilot study. World Journal of Gastroenterology: WJG 2015;21(10):3013.
6. Friedrich-Rust M, Rosenberg W, Parkes J, Herrmann E, Zeuzem S, Sarrazin C. Comparison of ELF, FibroTest and FibroScan for the non-invasive assessment of liver fibrosis. BMC gastroenterology 2010; 10(1):103.
7. Goertz RS, Sturm J, Pfeifer L, Wildner D, Wachter DL, Neurath MF, et al. ARFI cut-off values and significance of standard deviation for liver fibrosis staging in patients with chronic liver disease. Annals of Hepatology: Official Journal of the Mexican Association of Hepatology 2013;12(6).
8. Afdhal NH, Bacon BR, Patel K, Lawitz EJ, Gordon SC, Nelson DR, et al. Accuracy of fibroscan, compared with histology, in analysis of liver fibrosis in patients with hepatitis B or C: a United States multicenter study. Clinical Gastroenterology and Hepatology 2015;13(4):772-9. e3.
9. Nierhoff J, Ortiz AAC, Herrmann E, Zeuzem S, Friedrich-Rust M. The efficiency of acoustic radiation force impulse imaging for the staging of liver fibrosis: a meta-analysis. European radiology 2013; 23(11): 3040-53.
10. Sáez-Royuela F, Badia E. HEPATITIS C: IS REGRESSION OF ADVANCED FIBROSIS POSSI-

BLE AFTER TREATMENT? EMJ 2016;1(3):126-32.

11. Sáez-Royuela F, Linares P, Cervera LA, Almohalla C, Jorquera F, Lorenzo S, et al. Evaluation of advanced fibrosis measured by transient elastography after hepatitis C virus protease inhibitor-based triple therapy. European journal of gastroenterology & hepatology 2016;28(3):305-12.
12. Koh C, Heller T, Haynes-Williams V, Hara K, Zhao X, Feld JJ, et al. Long-term outcome of chronic hepatitis C after sustained virological response to interferon-based therapy. Alimentary pharmacology & therapeutics 2013;37(9):887-94.
13. Wedemeyer H, Dore G, Ward J. Estimates on HCV disease burden worldwide–filling the gaps. Journal of viral hepatitis 2015;22(s1):1-5.
14. Cobbold JF, Patel D, Taylor-Robinson SD. Assessment of inflammation and fibrosis in non-alcoholic fatty liver disease by imaging-based techniques. Journal of gastroenterology and hepatology 2012; 27(8): 1281-92.
15. Kirk GD, Astemborski J, Mehta SH, Spoler C, Fisher C, Allen D, et al. Assessment of liver fibrosis by transient elastography in persons with hepatitis C virus infection or HIV–hepatitis C virus coinfection. Clinical Infectious Diseases 2009;48(7):963-72.
16. Vergara S, Macías J, Rivero A, Gutiérrez-Valencia A, González-Serrano M, Merino D, et al. The use of transient elastometry for assessing liver fibrosis in patients with HIV and hepatitis C virus coinfection. Clinical Infectious Diseases 2007;45(8):969-74.
17. Tang A, Cloutier G, Szeverenyi NM, Sirlin CB. Ultrasound elastography and MR elastography for assessing liver fibrosis: part 2, diagnostic performance, confounders, and future directions. American journal of roentgenology 2015;205(1):33-40.

AN EXPERIENCE OF TOTAL THYROIDECTOMY IN BENIGN AND MALIGNANT THYROID DISORDERS AT SIR GANGA RAM HOSPITAL FJMU LAHORE

Liaquat Ali Bhatti,[1] Muhammad Aslam Javed,[2] Muhammad Arshad[3]

How to cite: Bhatti LA, Javed MA, Arshad M. An experience of total thyroidectomy in benign and malignant thyroid disorders at Sir Ganga Ram Hospital FJMU Lahore. JAIMC. 2021; 19(1): 56-60.

Abstract

Background: Total thyroidectomy is increasingly being preferred by most surgeons for patients with benign and malignant thyroid disorders, mainly due to higher incidence of recurrence and high complications rate associated with recurrent thyroid surgery after subtotal/near total thyroidectomy. The current research intends to testify the superiority of total thyroidectomy over subtotal/near total thyroidectomy and to evaluate the occurrence of transient or permanent postoperative recurrent laryngeal nerve (RLN) damage, permanent hypoparathyroidism, post-operative bleeding, seroma formation and wound infections after total thyroidectomy in benign and malignant thyroid disorders at a tertiary care hospital of Central Punjab.

Methodology: All consecutive patients who underwent total thyroidectomy surgery at Department of Surgery Unit II, Sir Ganga Ram Hospital, Lahore from November 2018 to February 2020 were enrolled for intra-operative and post-operative complications. Demographic data, intraoperative details, and postoperative outcomes of all patients who underwent total thyroidectomy were collected. Patients who had vocal cord palsy as assessed by preoperative fiber optic laryngoscopy were not included in this study, patients who had hypocalcaemia were also excluded.

Results: A total of 50 patients underwent total thyroidectomy during this study period. There were 8 male patients (16%) and 42 females (84%), with male to female ratio of 1:5. The age range was 20-60 years with mean age of patients was 35.6 years (5.65±SD). Amongst 50 patients, 31 had benign euthyroid multinodular goiter, 4 had Graves' disease, 6 had secondary hyperthyroidism, 2 had euthyroid recurrent multinodular goiter, 4 had papillary carcinoma and 3 had follicular carcinoma of thyroid gland. After total thyroidectomy neuroprexia was seen in 4(8%) patients, permanent RLN damage in 1 (2%) patient, permanent hypoparathyroidism in 1 (2%) patient, temporary hypoparathyroidism in 8 (16%), postoperative bleeding in 3 (6%) and postoperative seroma formation in 1 (2%) patient.

Conclusion: Total thyroidectomy is a preferable and safer option in various thyroid pathologies where surgery is indicated and is also associated with a low incidence of complications and morbidity along with less chances of recurrence.

Key Words: Recurrent laryngeal nerve injury, total thyroidectomy, hypoparathyroidism, hypocalcaemia.

Thyroid gland diseases are one of the most commonly seen endocrine disorders worldwide.[1] The thyroid gland is a small endocrine gland which produces thyroid hormones that regulates numerous metabolic activities of the body.[1] The principal diseases of the thyroid gland are hypothyroidism, hyperthyroidism, thyroiditis, multinodular goiter, recurrent multinodular goiter, Graves' disease with diffuse goiter, solitary nodule of thyroid and thyroid neoplasms which include papillary, follicular, medullary and anaplastic carcinoma of thyroid gland.[1] Total thyroidectomy has the advantage of reducing the risk of relapses and complication rates

1. Liaquat Ali Bhatti
2. Muhammad Aslam Javed
3. Muhammad Arshad

1. Fatima Jinnah Medical University Lahore
2,3. Department of Surgery, Fatima Jinnah Medical University Lahore

Correspondence:
Dr. Liaquat Ali Bhatti, *Associate Professor, Department of Surgery, Fatima Jinnah Medical University Lahore.*
Email: liaquatali9788@gmail.com

Submission Date: 20-10-2020
1st Revision Date: 29-11-2020
Acceptance Date: 06-12-2020

associated with second surgery, and hence an increasing number of total thyroidectomies are currently being performed worldwide for both benign and malignant thyroid pathologies.[2] Total thyroidectomy is defined as the removal of all thyroid tissue, with preservation of parathyroid glands and recurrent laryngeal nerves bilaterally.[3] This study was carried out to find out the safety profile of total thyroidectomy surgery in patients having both benign and malignant thyroid conditions.

METHODOLOGY

A single center, prospective study was conducted in the Surgical Unit II of Sir Ganga Ram Hospital, Lahore, affiliated with FJMU Lahore, to assess the incidence of intraoperative and postoperative complications of patients who underwent total thyroidectomy during November 2018 to February 2020. Demographic details of the patients were recorded. Both male and female patients who underwent total thyroidectomy procedure due to benign or recurrent multinodular goiter and neoplasms were included. Preoperative evaluation included clinical examination, routine pre-anesthetic assessment and investigations like thyroid function tests and serum calcium levels were done in all patients. To exclude pre-existing vocal cord palsy, an otolaryngologist assessed vocal cord motility preoperatively in all patients. Patients who had vocal cord palsy were excluded from study. Hyperthyroid patients were made euthyroid by giving antithyroid drugs and beta blockers. During surgery recurrent laryngeal nerve was identified (see Figure 1) and followed throughout its course from tracheoesophageal groove to its entry into the larynx on both sides. Both superior and inferior parathyroid glands were identified. Inferior thyroid artery was ligated in continuity to preserve blood supply of parathyroid glands. Factors such as safety, outcome of the surgery, and postoperative complications related to thyroidectomy like neuroprexia, permanent RLN damage either unilateral or bilateral, permanent hypoparathyroidism, seroma formation and wound infections were evaluated. Recurrent laryngeal nerve palsy was defined as hoarseness associated with vocal cord paralysis at laryngoscopy within 6 months postoperatively. After 6 months, recurrent laryngeal nerve palsy is considered to be permanent.[4]

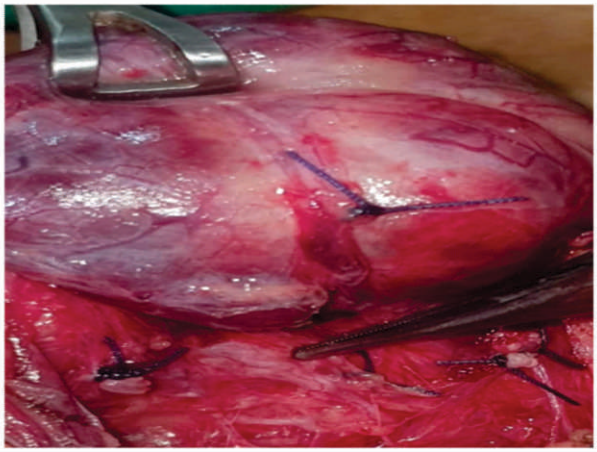


Figure 1: *Showing RLN after Dissection*

RESULTS

Between November 2018 and February 2020, 50 patients underwent total thyroidectomy. Of these, 8 were men and 42 were women (ratio 1:5). The age range was 20-60 years and mean age of patients was 35.6 years (5.65±SD). Diagnoses before surgery were benign euthyroid multinodular goiter in 31 patients (62%), Graves' disease in 4 patients (8%), secondary hyperthyroidism in 6 (12%), euthyroid recurrent multinodular goiter in 2 (4%), papillary carcinoma in 4 (8%) and follicular carcinoma of thyroid gland in 3 patients (6%). (Table 1).

Table 1: *Thyroid Pathology in Patients who Underwent Total Thyroidectomy (n=50)*

Pathology	% of Patients	Male	Female
Benign Euthyroid Multinodular Goiter	31(62%)	4(8%)	27(54%)
Graves' Disease	4(8%)	1(2%)	3(6%)
Secondary hyperthyroidism	6(12%)	2(4%)	4(8%)
Recurrent Multinodular Goiter	2(4%)	2(4%)	0(0%)
Papillary Carcinoma Of Thyroid	4(8%)	1(2%)	3(6%)
Follicular Carcinoma Of Thyroid	3(6%)	1(2%)	2(4%)

The most common indication for thyroid surgery was benign multinodular goiter involving

both lobes (n = 31, 62%). Preoperative laryngoscopy in all patients showed normal vocal cord motility and all were having normal serum calcium levels before surgery. Recurrent laryngeal nerve palsy occurred in 5 patients (10%); permanent unilateral recurrent laryngeal nerve palsy occurred in 1 patient (2%) and neuroprexia in 4 patients (8%). The patient with permanent RLN injury had recurrent multi nodular goiter disease after subtotal thyroidectomy and he was followed up for voice changes and his voice improved after 9 months due to compensation from contralateral vocal cord. Transient recurrent laryngeal nerve palsy (neuroprexia), resolving within 3 months, occurred in 4 patients (8%). Temporary hoarseness was more common among patients with multinodular goiter disease. No patient had transient or permanent bilateral recurrent laryngeal nerve palsy. Permanent hypoparathyroidism occurred in 1(2%) female patient with large benign multinodular goiter and temporary hypoparathyroidism was seen in 8 (16%) patients. Postoperative bleeding requiring surgical hemostasis occurred in 3 (6%) patients. Amongst these 3 patients, one patient had bleeding on table after extubation and was explored under anesthesia and bleeding vessel was ligated (inferior thyroid artery). The other two patients who developed neck swelling and difficulty in breathing in the evening of surgery in the ward, were explored in emergency and the bleeding vessels (one had bleeding from middle thyroid vein and other from inferior thyroid vein) were ligated. Postoperative seroma formation occurred in 1(2%) patients. No wound infection occurred in any of our patient (Table: 2 &

Table 2: *Complications After Total Thyroidectomy (n=50)*

Complication	No. of patients	Male	Female
Neuroprexia	4(8%)	1(2%)	3(6%)
Unilateral RLN palsy (permanent)	1(2%)	0	1(2%)
Hypoparathyroidism (permanent)	1(2%)	0	1(2%)
Hypoparathyroidism (temporary)	8(16%)	2(4%)	6(12%)
Postoperative bleeding	3(6%)	1(2%)	2(4%)
Seroma formation	1(2%)	0	1(2%)
Wound infection	0	0	0

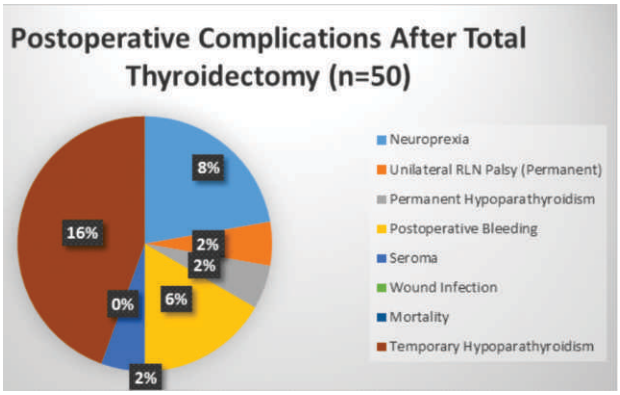


Figure 2: No postoperative mortality was seen during the study.

DISCUSSION

The frequency of total thyroidectomy being carried out for various thyroid disorders has expanded significantly in last few years.[2] There is increasing acknowledgment that total thyroidectomy is the suitable surgical treatment choice for both benign and malignant thyroid neoplasms.[2] The main advantage of total thyroidectomy over subtotal or near total thyroidectomies is the rapid relief of patient´s symptoms; provision of an adequate definite histopathological diagnosis, particularly when the clinical features are suggestive of the possibility of thyroid neoplasm (the reported risk in various case studies is nearly 5%–10%); and no potential risk of disease relapse.[5] Whereas in subtotal thyroidectomy or unilateral lobectomy, residual thyroid tissue is left behind, so the patient is exposed to a greater risk of disease relapse (23%–45%).[4] These patients with recurrent multi nodular goiter fails to respond to thyroxin suppression therapy and then ultimately will end up in repeat surgery.[6] Subtotal or near total thyroidectomy procedures does not reduce the potential risk of postoperative complications.[7] During repeat surgery the risk of injuring the recurrent laryngeal nerve is higher due to the presence of the fibrotic scarred tissue which would be left after the initial surgery.[8] There are various case studies of increase rates of transient (15.5% to 23.6%) and permanent (2.6% to 15.5%) recurrent laryngeal nerve damage after repeat thyroidectomy.[1] In our study on 50 patients who had total thyroidectomy surgery, tran-

sient recurrent laryngeal nerve palsy (Neuroprexia), resolving within 3 months, occurred in 4 patients (8%) and permanent unilateral recurrent laryngeal nerve palsy occurred in 1 patient (2%) only. On the other hand, the complication rates of subtotal thyroidectomy are similar to that of total thyroidectomy surgeries, and the complication risk of second surgery due to relapse is up to 20 times higher with subtotal thyroidectomy.[9] In our study the patient who had permanent RLN injury after total thyroidectomy had recurrent multi nodular goiter disease after subtotal thyroidectomy.

In a study conducted by Gough et al., recurrent laryngeal nerve palsy and permanent hypoparathyroidism after total thyroidectomy occurred at the rates of 0.7% and 2.2%, respectively.[2] In our study permanent unilateral recurrent laryngeal nerve palsy was seen in 2% patients, neuroprexia in 8% patients and permanent hypoparathyroidism in 2% patients and the results are almost comparable. Another study conducted by Efremidou et al., on 932 cases who underwent total thyroidectomy, the incidence of permanent unilateral recurrent laryngeal nerve palsy was 0.2%, whereas the incidence of neuroprexia was 1.3%.[7]

In a study by Jessie and Harrison1, the rate of temporary hypoparathyroidism ranged from 5 to 71% and permanent hypoparathyroidism ranged from 0 to 3.5%, while in our study the incidence of temporary hypoparathyroidism was 16% and permanent hypoparathyroidism was 2% which is showing that we are having better outcome in this regard.

The study conducted by Efremidou et al.,[7] on 932 cases, 2 patients (0.2%) had postoperative bleeding requiring surgical hemostasis and no wound infection was seen, whereas in our study postoperative hemorrhage occurred in 3 patients (6%) and no patient had wound infection postoperatively. Efremidou et al.,[7] also reported that hemostasis was achieved better after total thyroidectomies as compared to subtotal thyroidectomies.

Bage et al. 11 reported that for treating benign multinodular goiter and thyroid neoplasms, total thyroidectomy should be a preferable option, as it not only provides a definitive treatment of the disease, without carrying any risk of relapse, but also ensures complete relief of any compressive symptoms and comparably low risk of complications.

Our data also suggested that total thyroidectomy is a safer treatment option and can be carried out with minimum morbidity and low risk of complications among patients with benign and malignant thyroid disorders. Moreover, complication risk decreases as the surgeon competency skill improves. Also patient satisfaction and acceptance along with cosmetic outcome is also better achieved with total thyroidectomy as compared to subtotal thyroidectomy.

CONCLUSION

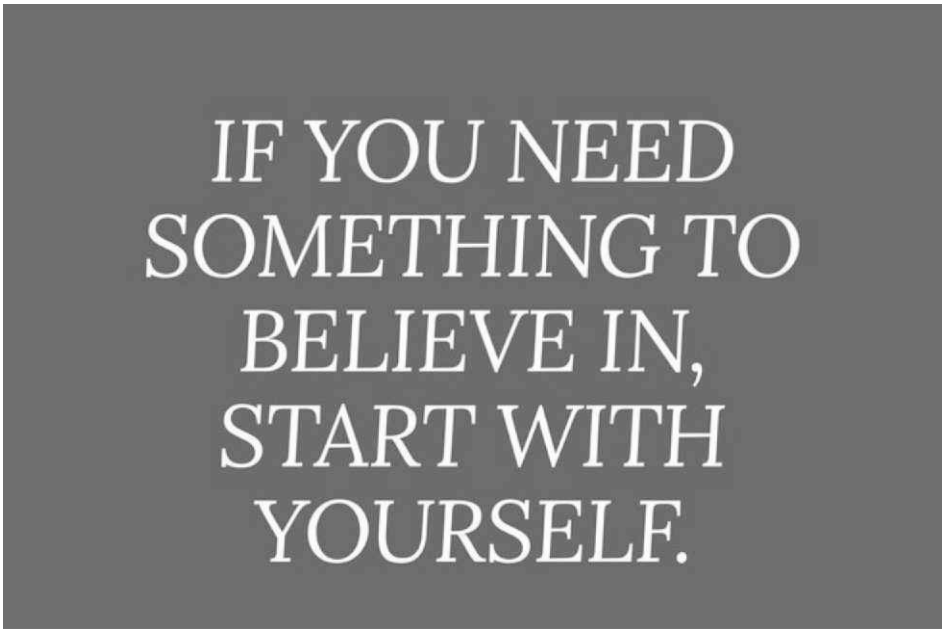
Subtotal thyroidectomy is associated with significant relapses and there is a possibility that it also might left behind a few regions of incompletely removed thyroid neoplasms, thus leading to postoperative complications and morbidity. Therefore it is concluded from our study that total thyroidectomy is a safer and preferred procedure for both benign and malignant thyroid conditions in the hands of a skilled surgeon.

REFERENCES

1. Padur AA, Kumar N, Guru A, Badagabettu SN, Shanthakumar SR, Virupakshamurthy MB, et al. Safety and Effectiveness of Total Thyroidectomy and Its Comparison with Subtotal Thyroidectomy and Other Thyroid Surgeries: A Systematic Review. J Thyroid Res. 2016;2016:7594615.
2. Gangappa RB, Kenchannavar MB, Chowdary PB, Patanki AM, Ishwar M. Total Thyroidectomy for Benign Thyroid Diseases: What is the Price to be Paid? J Clin Diagn Res.2016;10(6):04–07.
3. Dawei Hou, Haie Xu, Bing Yuan, Jianhui Liu, Yibing Lu, Ming Liu & Zhuyin Qian. Effects of active localization and vascular preservation of inferior parathyroid glands in central neck dissection for papillary thyroid carcinoma. World J Surg Oncol. 2020;18:352.
4. Pantvaidya G, Mishra A, Deshmukh A, Pai PS, D'Cruz A. Does the recurrent laryngeal nerve

recover function after initial dysfunction in patients undergoing thyroidectomy? Laryngoscope Investig Otolaryngol.2018;3(3):249–52.

5. Haugen BR, Sawka AM, Alexander EK, Bible KC, Caturegli P, Doherty GM, et al. American Thyroid Association Guidelines on the Management of Thyroid Nodules and Differentiated Thyroid Cancer Task Force Review and Recommendation on the Proposed Renaming of Encapsulated Follicular Variant Papillary Thyroid Carcinoma Without Invasion to Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features. Thyroid. 2017; 27(4):481-83.
6. Barczyński M, Konturek A, Hubalewska-Dydejczyk A, Gołkowski F, Nowak W. Ten-Year Follow-Up of a Randomized Clinical Trial of Total Thyroidectomy Versus Dunhill Operation Versus Bilateral Subtotal Thyroidectomy for Multinodular Non-toxic Goiter. World J Surg. 2018;42:384–92.
7. Ferrés CS, Martos ID, Navarrete NR, et al. Main care to avoid complications associated with thyroidectomy. Int J Fam Commun Med. 2019; 3(5): 227-34.
8. Joliat GR, Guarnero V, Demartines N, Schweizer V, Matter M. Recurrent laryngeal nerve injury after thyroid and parathyroid surgery; Incidence and postoperative evolution assessment. Medicine (Baltimore). 2017;96(17):e6674.
9. Yoldas T,Makay O, Icoz G, Kose T, Gezer G, Kismali E, et al. Should Subtotal Thyroidectomy Be Abandoned in Multinodular Goiter Patients From Endemic Regions Requiring Surgery? Int Surg. 2015; 100(1): 9–14.
10. Bage AM & Kalatharan P. Role of Total Thyroidectomy in Painful (Symptomatic) Hashimoto's Thyroiditis: Descriptive Study. Indian J Otolaryngol. 2020;17:40-01.



INTERRELATIONSHIP OF CIRCULATING BIOCHEMICAL MARKERS OF PROGNOSTIC IMPORTANCE IN PREGNANT FEMALES SUFFERING FROM ASTHMA

Madiha Ashraf,[1] Ameena Nasir,[2] Muhammad Faisal Javaid,[3] Maria Anwar,[4] Abdul Basit Ali[5]

How to cite: Ashraf M, Nasir A, Javaid MF, Anwar M, Ali AB. Interrelationship of circulating biochemical markers of prognostic importance in pregnant females suffering from asthma. JAIMC. 2021; 19(1): 61-65.

Abstract

Backgroud: Asthma is identified by the chronic inflammation of airway and bronchial hyperactivity involving the imbalance between the production of reactive oxygen species and the activity of antioxidants in cellular system. This imbalance activity is correlated with severity of the disease. The oxidative stress markers are modulated to specific pathophysiological alteration in respiratory tract as a result of formation of pro-inflammatory molecules such as PAF like lipid and isoprostanes.

Methodology: Fifty asthmatic pregnant female's subjects/Patients were eligible for inclusion in the study at Jinnah Hospital Lahore. Twenty age and sex-matched clinically apparently healthy individuals were included as controls. They were analyzed for their stress markers, vitamins and lipid profile.

Results: Significantly decreased level of both enzymatic and non-enzymatic antioxidants CAT, GSH and SOD, vitamin E and vitamin A were estimated in asthmatic group in comparison with normal individuals while concentration of Malondialdehyde (MDA) and Nitric oxide (NO) was elevated in disease group. Hormone profile indicated significantly elevated progesterone concentration while the levels of estrogen were decreased. Lipid profile was also differed significantly in both groups.

Conclusion: Performed research work concludes that asthmatic pregnant women present a positive relation among disease progression and oxidative stress. It is characterized by decreased levels of antioxidants i.e., SOD, CAT and some vitamins (E and C). Moreover, GSH was increased as compared to healthy women. Increased level of MDA signifies increased lipid peroxidation in the subjects of asthma. Level of electrolytes (K, Ca, Mg and P) was also disturbed in the asthmatic patients.

Key Words: Asthma, Oxidative stress, lipid profile, isoprostane, Blood sample.

Asthma is a non-contagious chronic ailment having multiple negative impacts on health, social and economics in the society. It involves hyperactive airways, reversible bronchial narrowing, bronchial smooth muscle thickening, airway remodeling and obstruction associated with paroxysmal or persistent symptoms including, cough and sputum production, breathlessness, wheezing and chest tightness.[1] It is the most predominant problem affecting pregnancy outcomes worldwide, having prevalence ranging from 8 to 10%.[2] The remarkable stimulators of asthmatic symptoms consist of contact to aeroallergens, bronchial infections, smoking, physical exercises and of particular concern pregnancy.[3] It complicates pregnancy and can cause premature birth, reduced birth weight, intrauterine growth restriction, pre-eclampsia and gestational diabetes.[4] The enlarged uterus in pregnancy uplifts the diaphragm about 4cm which leads to reduction in FRC (Functional residual capacity) and FEV1 (Forced expiratory volume).[5]

1. Madiha Ashraf
2. Ameena Nasir
3. Muhammad Faisal Javaid
4. Maria Anwar
5. Abdul Basit Ali

1. *PGMI/ Ameer-ud- Din Medical College Lahore*
2. *Allama Iqbal Medical College Lahore*
3. *Niazi Medical College Sargodha*
4. *Independent Medical College Faisalabad*
5. *Azra Naheed Medical College Lahore*

Correspondence:
Dr. Madiha Ashraf, *Associate Professor of Physiology, PGMI/ Ameer-ud- Din Medical College Lahore*

Submission Date: 09-11-2020
1st Revision Date: 20-11-2020
Acceptance Date: 29-11-2020

It has been well reported that excessive reactive oxygen molecules (ROMs) generation due to deranged balance of anti-oxidants produces airway inflammation, resulting in epithelial cell apoptosis thus, contribute in asthma.[6] Oxidative injury has been revealed at the maternal-fetal border and as the pregnancy proceeds, the production of oxidative stress markers is enhanced.[7] ROMs combine with low density lipoprotein (LDL) to form oxidized low density lipoprotein (Ox-LDL) which causes aggravation of placental progesterone and estrogen levels resulting in raised thyroid binding globulin and tri-iodothyronine, playing important role in abnormal pregnancy outcomes.[8] The higher levels of NO in early pregnancy mediate increased blood flow due reduction in resistance by vasodilation, thus hyperoxia results in hampering the development of placental villi and angiogenesis leading to life threatening problems for preterm.[9] On contrary to it, reduced maternal NO levels due to reduced glutathione resulting in bronchial smooth muscle contraction leading to asthma. The higher levels of oxytocin mediate increased calcium influx into the myometrial cells causing premature uterine contractions and preterm labor.[10] The aim and objectives of the present study were to assess the interrelationship of circulating biochemical markers of prognostic importance in pregnant females suffering from asthma.

METHODOLOGY

Fifty asthmatic pregnant females' subjects/ Patients were eligible for inclusion in the study at Jinnah Hospital Lahore. Detailed history, clinical examinations and if any, were collected from subjects of the study, by giving them a questionnaire. Twenty age and sex-matched clinically apparently healthy individuals were included as controls. Blood samples were collected with aseptic precaution. Informed consent from subjects was obtained before collection of blood samples. 5ml of blood was drawn from each patient.

All protocols were approved by research ethical committee of Institute of Molecular Biology and Biotechnology (IMBB), University of Lahore. Blood samples were centrifuged at 4000 rpm for 15 minutes and serum was separated in separate tubes. Blood GSH was estimated according to the method of Moron.,et al.[11] While Catalase was assa-yed according to the method of Aebi. Method of Ohkawa., et al.[12] was used for calorimetric determination of Lipid peroxidation in blood by using Thiobarbituric acid reactive substances (TBARS). Superoxide dismutase (SOD) activity was determined by the method of Kakkar.[13] Calcium ions (Ca^{2+}) were analyzed by using the method of Barnett in which Calcium form a violet complex with O-Cresolphthaline complexon in an alkaline medium. Lipid profile including LDL, HDL, T. Cholesterol and triglyceride were determined by using human cholesterol assay kit Abcam. Hormones including estrogen, progesterone, T3 and IL-6 and vitamin C and E were estimated by using commercially available Elisa kit.

RESULTS

The data presented in table 1 exhibit the upregulation of Malondialdehyde (MDA) in the group of subjects as compared to the healthy controls in controls the level of MDA remain (1.99±0.21 nmol/ml) while in patients it was significantly increased (3.98±0.38 nmol/ml., p=0.027), while the levels of antioxidants SOD, GSH, CAT were significantly decreased (0.46 ± 0.012 µg/ml, 5.78 ± 0.59 µg/ml, 1.66±0.18 nmol/mol of protein, p=0.056, 0.019, 0.034) as compared to healthy controls (0.55±0.017 µg/ml, 10.20±0.68 µg/ml, 3.26±0.23 nmol/mol of protein) respectively.

Low density lipoprotein (LDL), high density lipoprotein (HDL), total cholesterol (TCH) and triglyceride (Tg) differed significantly (≤0.05). LDL (2.65±0.13 mg/dl), TCH (6.35±0.34 mg/dl) and Tg (2.34±0.18 mg/dl) were recorded in asthmatic patients as compared to normal healthy controls LDL (2.35±0.09), TCH (5.26±0.29) and Tg (1.22± 0.16) mg/dl.

Levels of Estrogen and progesterone were

recorded in group of patients. Nitric oxide (NO) was recorded as (13.25±1.02 µm/L) in healthy subjects whereas it was significantly increased in group of asthmatic patients (17.05±1.22 µm/L). Level of estrogen was significantly decreased in the group of patients (12.29±1.99 pg/ml, p 0.015) as compared to healthy controls (21.26±2.26 pg/ml), whereas, the level of progesterone was significantly higher in the asthmatic group (88.19±4.29 ng/ml, p 0.001) as compared to healthy controls (55.88±5.26 ng/ml).

Levels of T3, IL-6 and Ca2+ were significantly higher (1.77±0.06 µg/dl, 5.16±1.29 pg/ml and 10.21 ± 2.16 mg/dl, p=0.014, 0.011, 0.001) as compared to healthy controls (1.35±0.05 µg/dl, 3.41±0.56 pg/ml, 6.91±1.08 mg/dl) respectively.

Table 1: *Circulating Biochemical Profile of Different Variables in Asthmatic Pregnant Females*

Variables	Control	Subjects	P-value
MDA nmol/ml	1.99±0.21	3.98±0.38	0.027
SOD µg/ml	0.55±0.017	0.46±0.012	0.056
GSH µg/ml	10.2±0.68	5.78±0.59	0.019
CAT nmol/mol of Prot.	3.26±0.23	1.66±0.18	0.034
TCH mg/dl	5.26±0.29	6.35±0.34	0.049
Tg mg/dl	1.22±0.16	2.34±0.18	0.456
LDL mg/dI	2.35±0.09	2.65±0.13	0.435
HDL mg/dI	2.05±0.25	1.33±0.18	0.034
Estrogen pg/ml	21.26±2.26	12.29±1.99	0.015
Progesterone ng/mI	55.88±5.26	88.19±4.29	0.001
T3 µg/dI	1.35±0.05	1.77±0.06	0.014
IL-6 pg/ml	3.41±0.56	5.16±1.29	0.011
Ca^{2+} mg/dJ	6.91±1.08	10.21±2.16	0.001
Vitamin E mg/dl	1.26±0.102	0.55±0.096	0.002
Vitamin C mg/dl	2.16±0.156	1.26±0.127	0.021
NO µm/L	13.25±1.02	17.05±1.22	0.013

Vitamins (E and C) present a highly significant difference comparing the study groups. The lower levels of vitamins (E and C) were recorded in asthmatic patients. The levels of vitamin E (0.55±0.096) and vitamin C (1.26±0.127), were calculated in asthmatic objects while these variables shows higher levels in controls (1.26±0.102) and (2.16±0.156) mg/dl respectively.

DISCUSSION

The present study showed that the pregnant females suffering from asthma have greater susceptibility to either preterm labor or abortion. This may be due to disturbed anti-oxidative status and raised allergy mediated up-regulation of pro-inflammatory cytokines. The resultant oxidative upset plays major role in the derangement of hormonal and lipid profile making the asthmatics more prone to fetal loss. The higher levels of calcium also have a significant impact on myometrium contraction by mediating the interaction of actin/myosin complex resulting in uterine contractions and preterm labor. It has been revealed that asthma leads to a considerable oxidative stress that can be indicated by the high levels of MDA and low levels of antioxidant enzymes, therefore measuring MDA levels is an important indicator of lipid peroxidation in severe asthmatics. Superoxide dismutase depicts both anti-oxidative and anti-inflammatory properties, thus playing a crucial role in asthma because it results in the production of pro-inflammatory cytokines (SOD Vs IL-6, r=-0.663).

Table 2: *Pearson's Correlation Coefficients of Prognostic Variables in Asthmatic Pregnant Females*

VARIABLES	(r)	P-VALUE
8-OHdG Vs MMP-1	0.519*	0.0314
8-OHdG Vs MMP-2	0.465*	0.0253
8-OHdG Vs MMP-3	0.853***	0.0017
8-OHdG Vs MMP-8	0.661**	0.0140
8-OHdG Vs MMP-9	0.649**	0.0118
8-OHdG Vs MMP-10	0.667**	0.0356
IL-4 Vs MMP-3	0.795***	0.0056
IL-2 Vs MMP-3	0.619**	0.0314
IL-5 Vs MMP-3	0.786***	0.0000
TNF α Vs MMP-3	0.886***	0.0016
MMP-3 Vs TNF-α	0.773***	0.0038
MMP-3 Vs IL-1	0.646**	0.0041
IL-10 Vs MMP-3	0.749***	0.0153
MMP-3 Vs Neutrophils	0.896***	0.0000
MMP-2 Vs Neutrophils	0.674**	0.0161
MMP-3 Vs Cortisol	0.899***	0.0048
TNF-α Vs Cortisol	0.887**	0.0000
TNF-α Vs IL-2	0.746***	0.0034
Cortisol Vs IL-2	0.861***	0.0000

Glutathione has a major role in asthma as it is important in inhibiting mucin gene expression and airway hypersensitivity in cytokine dependent model of asthma I4. The lower levels of glutathione decreases nitric oxide (NO) bioavailability, having major role in bronchial smooth muscle relaxation (GSH Vs NO, r= 0.651). The deranged levels of antioxidants in asthmatic pregnant females cause inflammation which ultimately results in hormonal imbalance, especially increased progesterone levels due to the activation of hypothalamic pituitary gonad axis mediates premature rupture of membranes (PROM) leading to preterm labor.[15] The disequilibrium in anti-oxidative profile of asthmatics may be further affected by dietary lack of anti-oxidants like vitamin C and E, thus consequently results in enhanced apoptosis, detaching of airway epithelial cells and airway remodeling.[16] The deficient vitamin E can hamper IgE response and efficient T-lymphocyte activity.[17] It has been proposed that provision of vitamin C can rectify pulmonary function tests and alter airway geometry resulting in reduction of coughing and wheezing.[18]

Cholesterol transported from the intestine as chylomicrons is metabolized to form very low density lipoproteins (VLDL) in the liver. Once VLDL reaches the peripheral tissues it is hydrolyzed to form low density lipoproteins (LDL), therefore facilitating transfer of fatty acids from triglyceride in the LDL particle into the cells thru LDL cell membrane receptors.[19] In pregnancy, LDL levels are elevated and one of the reasons of our particular concern is increased progesterone which leads to rise in LDL levels, chief substrate for placental progesterone synthesis. Hepatic lipase activity and raised maternal estrogen levels are also responsible for a rise in LDL levels during pregnancy results in increased thyroid binding globulin and tri-iodothyronine (T3) (Estrogen Vs T3, r = 0.459) leading to uterine contraction and preterm labor.[20] It has been also suggested that there is up-regulation of estrogen receptors in stimulated eosinophils on allergic mucosa which further enhance the contractility of myometrium (Bonin et al., 1995). The increased progesterone also switches nascent T-helper cells (Th-0) to Th-2 cells, thus playing role in production of inflammatory cytokines (Progesterone Vs IL-6, r=0.539). It has been reported that HDL levels do not raise significantly in first trimester but in second trimester its levels may be raised upto 14mg/dl and then decline to 5mg/dl in third trimester.[21,22]

The present study also depicts a mild decrease in HDL levels of asthmatic females. Oxidative injury results in higher cortisol and oxytocin levels while on the other hand, there is up-regulation of oxytocin receptors.[23] Both of these effects lead to calcium influx by the activation of IP3/DAG pathway causing calcium to bind with calmodulin stimulates the myosin light chain kinase, important in the regulation of actin-myosin interaction mediating uterine contraction and preterm labor.[24] Calcium may bind to calmodulin and stimulates enzymes required for the synthesis of prostaglandins and leukotrienes causing smooth muscle spasm and ultimately leading to asthmatic episodes.[25] It has been revealed from the present study that by rectifying antioxidant and anti-inflammatory status in asthmatic females, the perturbed hormonal balance and lipid profile can be hampered thus, limiting the probability of abortion/ preterm labor.

CONCLUSION

Performed research work concludes that asthmatic pregnant woman presents a positive relation among disease progression and oxidative stress. It is characterized by decreased levels of antioxidants i.e., SOD, CAT and some vitamins (E and C). Moreover, GSH was increased in asthmatic pregnant woman as compared to healthy women. Increased level of MDA signifies increased lipid peroxidation in the subjects of asthma. Level of electrolytes (K, Ca, Mg and P) were also disturbed in the asthmatic patients. Hence different oxidative stress markers can be deployed as significant prognostic tools to hint at the progression of the disease in asthmatic pregnant woman.

REFERENCES

1. Nguyen VT and Tran TH. Improved treatment of Asthma by using natural sources of antioxidants. Springer Plus 2013; 2-278.
2. Ali Z, Ulrik CS. Incidence and risk factors for exacerbations of asthma during pregnancy. Journal of Asthma and Allergy 2013; 6:53-60.
3. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhino conjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multi country cross-sectional surveys. Lancet 2006; 368: 733-43.
4. Gutaj P, Wender-Ozegowska E. Diagnosis and Management of IUGR in Pregnancy. Complicated by Type 1 Diabetes Mellitus. Current Diabetes Reports 2016; 16:39.
5. Dombrowski MP, M Schatz, R Wise. Asthma during pregnancy. Obstet Gynecol 2006; 103:05-12.
6. Cho YS, Moon HB. The Role of Oxidative Stress in the Pathogenesis of Asthma. Allergy, Asthma & Immunology Research 2010; 2(3):183-187.
7. Toescu V, Nuttall SL, Martin U, Kendall MJ, Dunne F. Oxidative stress and normal pregnancy. Clin Endocrinol (Oxf) 2002; 57(5):609-13.
8. Ain KB, Refetoff S, Sarne DH, Murata Y. Effect of estrogen on the synthesis and secretion of thyroxine-binding globulin by a human hepatoma cell line, Hep G2. Mol Endocrinol 1988; 2(4):313-23.
9. Ilekis JV, Tsilou E, Fisher S, Abrahams VM, Soares MJ, Cross JC. Placental origins of adverse pregnancy outcomes: potential molecular targets. An Executive Workshop Summary of the Eunice Kennedy Shriver National Institute of Child Health and Human Development 2016; S1-S46.
10. Amrani Y, Syed F, Huang C. Expression and activation of the oxytocin receptor in airway smooth muscle cells: Regulation by TNFα and IL-13. Respiratory Research 2010; 11(1):104.
11. Moron MS, Depierre JW, Mannervik B. Levels of glutathione reductase and glutathione S-transferase in rat lung and liver. Biochem Biophysic Acta 1979; 582:67-8.
12. Ohkawa H, Ohishi N, Yagi K. Assar for lipid peroxides in animal tissues by thiobarbituric acid reaction. J Anal Biochem 1979; 351-58.
13. Kakkar PB, Das P, Vishwanathan PN. A modified spectrophotometer assay of superoxide dismutase. Ind J Biochem Bio 1984; 21:130-32.
14. Fitzpatrick AM, Jones DP, Brown LAS. Glutathione Redox Control of Asthma: From Molecular Mechanisms to Therapeutic Opportunities. Antioxidants & Redox Signaling 2012; 17(2):375-408.
15. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med. 2000; 342:1500-1507.
16. Moreno-Macias H, Romieu I. Effects of antioxidant supplements and nutrients on patients with asthma and allergies. J Allergy Clin Immunol 2014; 133: 1237-44.
17. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. Nature reviews Immunology 2008; 8(9):685-698.
18. Niimi A. Cough and Asthma. Current Respiratory Medicine Reviews 2011; 7(1):47-54.
19. Barochia AV, Kaler M, Cuento RA, Gordon EM, Weir NA, Sampson M et al. Serum Apolipoprotein A-I and Large High-Density Lipoprotein Particles Are Positively Correlated with FEV1 in Atopic Asthma. American Journal of Respiratory and Critical Care Medicine 2015; 191(9):990-1000.
20. Pecks U, Rath W, Kleine-Eggebrecht N. Maternal Serum Lipid, Estradiol, and Progesterone Levels in Pregnancy, and the Impact of Placental and Hepatic Pathologies. Geburtshilfe and Frauenheilkunde 2016; 76(7):799-808.
21. David ML and Serpil CE. Asthma and Allergy. Cleveland Clinic Publications, E Pub 2010; 12-17.
22. Yiallouros PK, Savva SC, Kolokotroni O, Dima K, Zerva A, Kouis P et al. Asthma: the role of low high-density-lipoprotein cholesterol in childhood and adolescence. Int Arch Allergy Immunol 2014; 165(2): 91-9.
23. Robinson RS, Mann GE, Lamming GE, Wathes DC. Expression of oxytocin, oestrogen and progesterone receptors in uterine biopsy samples throughout the oestrous cycle and early pregnancy in cows. Reproduction 2001 Dec; 122(6):965-79.
24. Arthur P, Taggart MJ, Mitchell BF. Oxytocin and parturition: a role for increased myometrial calcium and calcium sensitization? Front Biosci 2007; 12: 619-33.
25. Kuo KH, Dai J, Seow CY, Lee CH, van Breemen C. Relationship between asynchronous Ca2+ waves and force development in intact smooth muscle bundles of the porcine trachea. Am J Physiol Lung Cell Mol Physiol 2003; 285:L1345-L1353.

EFFECT OF NARROW BAND ULTRAVIOLET B PHOTOTHERAPY ON SERUM FOLIC ACID LEVEL

Nadia Ali Azfar,[1] Wasfa Hayat,[2] Sadaf Amin,[3] Ammara Rafaqat,[4] Muhammad Nadeem,[5] Tariq Rashid[6]

How to cite: Azfar NA, Hayat W, Amin S, Rafaqat A, Nadeem M, Rashid T. Effect of narrow band ultraviolet B phototherapy on serum folic acid level. JAIMC. 2021; 19(1): 66-68.

Abstract

Background: Narrowband ultraviolet B phototherapy (NB-UVB) is a widely used therapeutic modality in the treatment of psoriasis vulgaris, atopic dermatitis, mycoses fungoides and many other dermatoses. It is generally accepted as safe in pregnancy and women of child bearing age. Several studies have shown photo inactivation of serum folate levels after exposure to UVA radiation but the effect of UVB radiation therapy is not known. We studied the effect of NB-UVB phototherapy on serum folic acid levels in patients with various dermatological conditions.

Objective: To evaluate the effect of Narrowband UVB phototherapy on serum folate levels.

Methodology: A multi-center, prospective, open observational study was carried out on eighteen patients undergoing Narrowband UVB phototherapy for various skin conditions. Serum folic acid levels were evaluated at baseline and after 36 Narrow band UVB therapy sessions i. e three sessions per week for 3 months.

Results: A total number of eighteen patients were enrolled with 7 males and 11 females. The mean age of patients was 31 years (5.65±SD). After 36 sessions of NB-UVB phototherapy a significant decrease of serum folate level was observed from 98.12ng/ml to 72.51ng/ml. The mean decrease in serum folic acid level was 1.43ng/ml and the mean NB-UVB cumulative dose was 80.95±3.50 J/cm^2..

Conclusion: A significant decrease of serum folate levels was observed after Narrowband UVB phototherapy sessions.

Key Word: Narrowband UVB, serum folate levels

Phototherapy is indicated in the treatment of numerous inflammatory dermatological conditions which include psoriasis vulgaris, vitiligo, lichen planus, atopic dermatitis and mycosis fungoides.[1] Narrow band UVB phototherapy does not require the administration of a photosensitizer, in contrast to PUVA (psoralen with ultraviolet A) thus making it a preferable therapeutic approach.[2] UVB phototherapy is also a safer therapeutic option in patients in whom systemic treatment cannot be administered such as pregnant women, patients with severe renal disease, liver pathology or malignancies.[2]

Several in vitro studies have suggested folate inactivation by ultraviolet exposure.[3] Folate deficiency is also associated with fetal neural tube defects, cardiac abnormalities and facial cleft in women of child bearing age.[3] Folic acid deficiency may also be associated with increased risk of colorectal malignancy, and might also affect serum homocysteine levels, which is thought to be a risk factor for cardiovascular disease, dementia and depression.[3] The objective of the present prospective study was to assess serum folate level's relation with Narrowband UVB exposure in our Asian population.

1. Nadia Ali Azfar
2. Wasfa Hayat
3. Sadaf Amin
4. AmmaraRafaqat
5. Muhammad Nadeem
6. Tariq Rashid

1,3,5: Department of Dermatology, Fatima Jinnah Medical University/ Sir Ganga Ram Hospital, Lahore

2,4,6: Department of Dermatology, Allama Iqbal Medical College/ Jinnah Hospital, Lahore

Correspondence:
Dr. Nadia Ali Azfar, Associate Professor, Dermatology, Fatima Jinnah Medical University, Lahore

Submission Date: 08-11-2020
1st Revision Date: 28-11-2020
Acceptance Date: 12-12-2020

METHODOLOGY

The study was carried out in the Dermatology Departments of Jinnah Hospital Lahore and Sir Ganga Ram Hospital, Lahore between October 2018 and July 2019. A total of eighteen patients were enrolled who were undergoing Narrowband UVB therapy for various dermatological conditions. An approval from the Institutional Ethical Committees was obtained, and written informed consent was taken from all enrolled patients. Demographic details of the patients were recorded. The patients who were on drugs that interfere with folic acid metabolism or an underlying pathology with abnormal folate metabolism (e.g. thalassemia minor or major), pregnant females at the onset of phototherapy, patients with history of alcohol consumption and non-compliant patients were not included. Baseline blood samples for serum folic acid levels were taken before phototherapy and after 36 sessions of Narrowband UVB exposures. Serum folate levels were determined using Elisa method. Narrowband UVB was given using a Waldmann UV-7002 cabinet equipped with twelve NB-UVB TL-01 fluorescent tubes, 3 times per week for a total of 36 sessions. The starting Narrowband UVB dose was selected according to the patient's skin photo type and ranged between 0.3 and 0.6 J/cm.[2] Dose increments of 10–20% were given at each session till minimal erythema dose was achieved.

RESULTS

A total of eighteen patients who met the inclusion criteria were enrolled. There were 7 males and 11 female patients with an age range of 6 to 65 years. The mean age of patients was 31 years (± 5.65) The most common conditions for Narrowband UVB phototherapy were psoriasis, eczema and vitiligo. There were 3 sessions in a week. All the enrolled patients completed 36 sessions of Narrowband UVB phototherapy during a period of 12 weeks. At baseline, the cumulative serum folic acid levels were 98.12ng/ml (mean 5.45ng/ml) and after 36 sessions of Narrowband UVB exposures it was decreased to 72.51ng/ml (mean 4.02ng/ml). After 36 exposures the mean decrease in serum folic acid level was 1.43ng/ml. The mean Narrowband UVB cumulative dose was80.95±3.50 J/cm.[2]

DISCUSSION

Folate is an essential nutrient also known as vitamin B9, required for the metabolism of amino acids and DNA synthesis. It is primarily found in the form of 5-methyltetrahydrofolate in leafy green vegetables, liver and fortified foods such as cereals and bread.[4] Reduced folic acid levels are associated with an increased risk for colorectal malignancy and in pregnant females, reduced levels may cause fetal congenital malformations such as neural tube defects, cardiac abnormalities and facial cleft.[3]

Narrowband UVB phototherapy is a widely accepted modality in the treatment ofnumerous skin conditions like psoriasis vulgaris, atopic eczema, vitiligo, lichen planus and mycosis fungoides.[5] Narrowband UVB phototherapy is considered safe for pregnant women in whom systemic therapy cannot be instituted and is considered the first-line therapy in pregnant females suffering from psoriasis vulgaris in whom systemic therapy is indicated.[6]

The action spectrum for folate molecule inactivation ranges from Ultraviolet C to Ultraviolet A spectrum with maximum degradation around 270 nm.[7] When folic acid molecule is exposed to ultraviolet radiations it is broken down into para-aminobenzoyl-L-glutamic acid and 6-formyl pterin.[2] The photo inactivation of folate after exposure to Narrowband UVB phototherapy is of great importance in psoriasis patients who already suffer from a low serum folate levels likely due to increased metabolism of folate by the hyper-proliferating cutaneous epidermal cells in psoriatic lesions.[6]

A study conducted by El-Saieet al., on 30 patients having psoriasis who underwent 12-36 sessions of Narrowband UVB phototherapy. After 36 sessions, the mean serum folate levels had decreased in 22 patients from baseline mean folate levels 8.64ng/ml to 6.32ng/ml after a mean NB-

UVB cumulative dose of 118.16 J/cm 2.8 Our study conducted on 18 patients with various dermatological conditions, who underwent 36 sessions of Narrowband UVB exposure revealed fall in serum folate levels from mean baseline 5.45ng/ml to 4.02ng/ml after a mean cumulative dose of 80.95± 3.50 J/cm^2, thus the results were almost comparable with their study.

In another study conducted by El-Borhamyet al. on 20 patients who completed 36 sessions of Narrowband UVB, serum folate levels were significantly reduced from baseline8.1ng/ml to5.9ng/ml after a cumulative dose of 75.95±3.67J/cm^2.[9]

It is generally seen that for the treatment of skin conditions with UVB phototherapy, folate supplementation is not routinely indicated but in high risk patients such as pregnant or lactating females and patients who are on folate lowering drugs, folic acid supplementation must be considered. In addition, studies with larger sample size should be conducted in our Asian population to better understand the relation of folate levels with UV exposure and to measure the RBC folate levels in addition to serum folate.

CONCLUSION

It is concluded from our study that exposure to high cumulative Narrowband UVB phototherapy can induce statistically significant folate catabolism. It is therefore suggested that for females with prolonged exposure to Narrowband UVB phototherapy for therapeutic reasons, adequate folic acid supplementation should be considered.

REFERENCES

1. Olsen EA, Hodak E, Anderson T, Henderson M, Cooper K, Lim HW. Guidelines for phototherapy of mycosis fungoides and Sézary syndrome: a consensus statement of the United States Cutaneous Lymphoma Consortium. J Am AcadDermatol. 2016; 74:27–58.
2. Weber B, Marculescu R, Radakovic S, Tanew A. Serum levels of folate, 25-hydroxyvitamin D3 and cobalamin during UVB phototherapy: findings in a large prospective trial. J EurAcadDermatol Venereol. 2020;34(2):385–91.
3. Zhang M, Goyert G, Lim HW. Folate and phototherapy: what should we inform our patients? J Am AcadDermatol.2017; 77:958–64.
4. Mahmood L. The metabolic processes of folic acid and Vitamin B12 deficiency. J Health Res Rev. 2014;1(1):5-9.
5. Ibbotson SH. A Perspective on the Use of NB-UVB Phototherapy vs. PUVA Photo chemotherapy. Front Med (Lausanne).2018;5:184.
6. Vena GA, Cassano N, Bellia G, Colombo D. Psoriasis in pregnancy: challenges and solutions. Psoriasis (Auckl). 2015; 5:83–95.
7. Juzeniene A, Tam Thu TT, IaniV, Moan J. The action spectrum for folic acid photo degradation in aqueous solutions. J PhotochemPhotobiol B. 2013; 126: 11–16.
8. Shaheen M, Fattah NA, El-Borhamy M. Analysis of serum folate levels after narrow band UVB exposure. Egypt Dermatol Online J. 2006;2:1–7.
9. El-Saie LT, Rabie AR, Kamel MI, Seddeik AK, Elsaie ML. Effect of narrowband ultraviolet B phototherapy on serum folic acid levels in patients with psoriasis. Lasers Med Sci. 2011; 26:481–5.

HIGHER SUPPLEMENTAL OXYGEN REQUIREMENT AT ADMISSION IS A MAJOR DETERMINANT OF MORTALITY AMONG COVID-19 PATIENTS

Shahrukh Rizvi,[1] Jahanzeb Rasheed,[2] Omair Farooq,[3] Atika Masood[4]

How to cite: Rizvi S, Rasheed J, Farooq O, Masood A. Higher supplemental oxygen requirement at admission is a major determinant of mortality among COVID-19 patients. JAIMC. 2021; 19(1): 69-74.

Abstract

Objective: Covid-19 has turned out to be a global pandemic and has affected people all over the world. It has troubled the physicians, researchers, and scientists in determining the most accurate pathway of disease management following which precious lives could be saved. This research is aimed at analyzing the importance of supplementary oxygen requirement at admission to hospital as a major determinant of morbidity and mortality among symptomatic Covid-19 patients.

Methodology: A retrospective cohort study was done on 280 patients admitted to Corona Wing of Farooq Hospital West Wood Lahore between April 2020 and August 2020. Multiple factors were found to be indicators of poor prognosis in Covid-19 patients. Patients' disease process and recovery was monitored starting at the time of presentation to hospital and keeping the target blood oxygen saturation more than or above 90% with or without supplementation. All the admitted patients were treated according to regularly updated local and international guidelines.

Results: Of the 280 patients admitted due to COVID-19, 82.9% survived whereas 17.1% died.

Higher supplemental oxygen requirement at the time of admission led to lower recovery rate and vice versa. Age of the patients and no. of co-morbidities were also directly proportional to poor prognosis. Higher supplementation led to longer hospital stay as well.

Conclusion(s): The supplemental oxygen requirement at the time of presentation can be considered a primary indicator to gauge the prognosis of worsening Covid-19 patients and also could play an important role in early management and better response to treatment.

Key Words: High supplement oxygen, mortality, COVID-19

Covid-19 has affected millions and has resulted in loss of almost a million lives worldwide. The high mortality of critically ill patients has largely been attributed to the fact that definitive treatment is yet to be discovered.

Although the in-hospital treatment guidelines are being updated regularly by experts however no breakthrough has yet been made and most of the management has based on supportive treatment rather than definitive. Also, it has been seen that the efficacy of the treatment is inversely proportional to the severity of disease. Therefore, recognizing the disease progression at an early stage is pivotal in prognosis.[1]

Initially Covid-19 can cause a variety of mild to moderate symptoms ranging from fever, cough, flu like symptoms, myalgias to digestive tract complains.[2,3] However, as the disease progresses to become severe, it can involve the lungs leading to the respiratory distress and subsequently the need for supplemental oxygen.[4,5]

Other factors have proven to dominate in

1. Shahrukh Rizvi
2. Jahanzeb Rasheed
3. Omair Farooq
4. Atika Masood

1,2. Farooq Corona Hospital, West Wood Branch Lahore
3. Medical Specialist, Farooq Corona Hospital, Lahore.
4. Akhtar Saeed Medical & Dental College, Lahore.

Correspondence:
Dr. Shahrukh Rizvi, *Medical Officer – ICU, Farooq Corona Hospital, Lahore. Farooq Hospital West Wood Branch Lahore*
Email: shahrukhrizvi186@gmail.com

Submission Date: 12-11-2020
1st Revision Date: 10-12-2020
Acceptance Date: 16-12-2020

determining the course and severity of disease in all the patients. Amongst those age, gender and co-morbidities have shown to play a significant role. Covid-19 has caused more severe disease in people from higher age group. Same is the case with males as females are seen to be less affected according to the data collected. The no of co-morbidities is directly proportional to disease severity and complications and inversely proportional to chances of recovery.[6,7]

The increasing disease severity leads to higher probability of need for ICU care and ultimately intubation. This sequalae is seen in this set of data and it also corroborates with the trend seen elsewhere.[8]

The research has shown that the respiratory distress in Covid-19 patients occurs because of cytokine storm due to immune response to the infection causing pulmonary infiltration.[9] It has been observed clinically that the extent of pulmonary infiltration has resulted in variable requirements of supplemental oxygen in patients and it is not a quantifiable factor. However, the supplemental oxygen requirement at a certain point of time is seen to be a better and quantifiable determinant of prognosis.

Among the 280 patients included in this study, it has been observed that patients who were admitted to the hospital with <5 liters per min supplemental oxygen requirement had the best prognosis with mortality rate of <14% whereas those who presented requiring ≥ 15 liters per min supplemental oxygen had a high mortality of >60%.

Although the ARDS is a feared sequela and guarantees a poor prognosis 10, the timely admission to hospital and appropriate treatment is pivotal in preventing the percentage of patients infected from reaching the critical stage. Hence early presentation and timely treatment can help in saving lives.

The objective of this study is to establish the link between supplemental oxygen requirement at presentation and end prognosis.

METHODOLOGY

This Retrospective Cohort Study included 280 of the patients admitted to Farooq Hospital Corona Wing Lahore.

The data was retrieved from hospital records at the end of said period i.e. April 2020 to August 2020.

Patients' oxygen saturation was monitored starting at the time of admission and supplemental oxygen was given where required to reach the set target of saturation of 92%. This initial supplemental oxygen requirement held the focal point in this discussion, patient's condition and recovery was followed while giving treatment according to regularly updated local and international guidelines. The relationship between supplemental oxygen at presentation and outcome of the patient was studied to

Table 1: *Table 1: Clinical and Gemographic Characteristics of Corona Virus Gisease 2019 (COVID-19) Patients*

Sex	
Male	225 (80.4%)
Female	55 (19.6%)
Age (years)	54.5 ± 14.5
Condition at admission	
Mild	86 (30.7%)
Moderate	57 (20.4%)
Severe	98 (35.0%)
Critical	39 (13.9%)
Days since hospitalized	8.65 ± 5.60
Co-morbidity	1.10 ± 0.99
0	96 (34.3%)
1	87 (31.1%)
2	73 (26.1%)
3	21 (7.5%)
4	3 (1.1%)
ICU care required	
No	206 (73.6%)
Yes	74 (26.4%)
Intubation required	
No	231 (82.5%)
Yes	49 (17.5%)
Supplemental Oxygen (L/min)	
No	143 (51.1%)
Mild (1 – 5)	67 (23.9%)
Moderate (6 – 15)	31 (11.1%)
High (> 15)	39 (13.9%)
Outcome	
Expired	48 (17.1%)
Discharged	232 (82.9%)

devise the relevance of the former in predicting the prognosis.

The study was approved by ethical committee of Farooq Hospital West Wood Lahore.

The data was analyzed using SPSS (v. 22.0). Mean and standard deviation were generated for age and days since hospitalization and were represented in the form of a table (Table 1). Categorical clinical and socio-demographic variables were represented as frequencies and percentages (see Table 1).

The levels of supplemental oxygen required at presentation was recoded into four categories: no requirement, mild requirement where supplemental oxygen delivered ranged '1–5 Liters/min', moderate requirement where supplemental oxygen delivered varied between '6–15 Liters/min', and high requirement where supplemental oxygen delivered was between '16 – 25 Liters/min' and included patients who were not maintaining 90% saturation even at supplemental oxygen administered at 25 Liters/min.

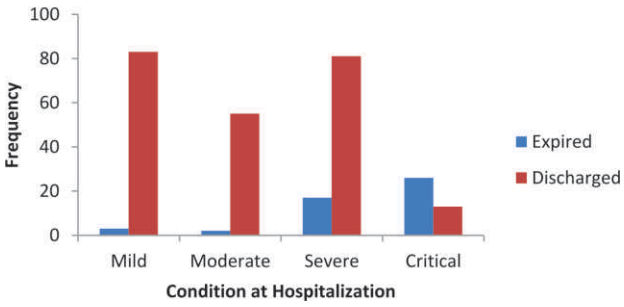
Table 2: *Comparison of Predictor Variables with Clinical Outcomes in Corona Virus Disease 2019 (COVID-19) Patients*

Variables	Expired	Discharged	*p*- value
Sex of patient			0.23
Male	42 (18.7%)	183 (81.3%)	
Female	6 (10.9%)	49 (89.1%)	
Age group			*< 0.001*
⩽ 40 years	1 (1.9%)	52 (98.1%)	
40 – 60 years	17 (13.7%)	107 (86.3%)	
⩾ 61 years	30 (29.1%)	73 (70.9%)	
Condition at Hospitalization			*< 0.001*
Mild	3 (3.5%)	83 (96.5%)	
Moderate	2 (3.5%)	55 (96.5%)	
Severe	17 (17.3%)	81 (82.7%)	
Critical	26 (66.7%)	13 (33.3%)	
Supplemental Oxygen (L/min)			*< 0.001*
No requirement	5 (3.5%)	138 (96.5%)	
Mild (1 – 5)	9 (13.4%)	58 (86.6%)	
Moderate (6 – 15)	9 (29.0%)	22 (71.0%)	
High (> 15)	25 (64.1%)	14 (35.9%)	
Number of co-morbidity			*< 0.001*
0	6 (6.3%)	90 (93.8%)	
1	15 (17.2%)	72 (82.8%)	
2	17 (23.3%)	56 (76.7%)	
3	8 (38.1%)	13 (61.9%)	
4	2 (66.7%)	1 (33.3%)	

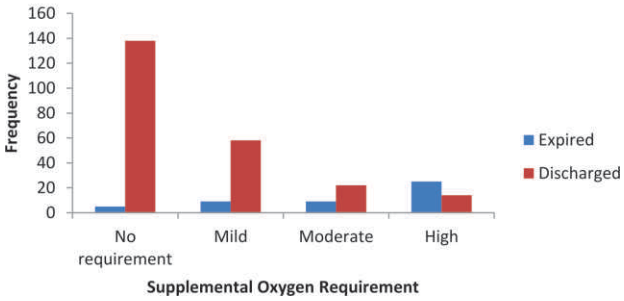
The variable of clinical outcome was recorded as '0' which meant expired and '1' which referred to patients who were successfully treated and discharged. Separate cross-tabulation were done to compare sex, age group, number of co-morbidity (see Table 2), condition at the time of admission (see Table 2 and Graph 1), and supplemental oxygen required during treatment (see Table 2 and Graph 2) with respect to clinical outcome (expired/discharged).

In order to see the differences in clinical outcomes with respect to condition at the time of hospitalization and supplemental oxygen administered, separate binary logistic regression analysis was

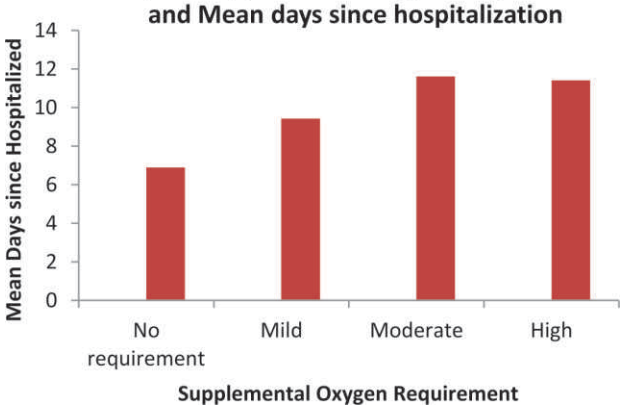
Graph 1 Condition at Hospitalization and Clinical Outcome in COVID-19 patients



Graph 2 Supplemental Oxygen Requirement and Clinical Outcome in COVID-19 patients



Graph 3 Supplemental Oxygen Requirement and Mean days since hospitalization



performed by adjusting for age, sex, days since hospitalization, and number of co-morbidity and the results are reported in Table 3.

Table 3: *Binary Logistic Regression of Condition at Hospitalization and Supplemental Oxygen Requirement with Clinical Outcomes in Corona Virus Disease 2019 (COVID-19) Patients*

Variables	AOR	95% CI	*p*-value
Age	0.96	0.93 – 0.99	$p < 0.01$
Sex			
Male	0.39	0.12 – 1.24	0.11
Female	1		
Co-morbidity	0.60	0.39 – 0.91	0.015
Days since hospitalization	1.01	0.95 – 1.08	0.75
Condition at Hospitalization			
Mild	1		
Moderate	1.53	0.24 – 9.87	0.65
Severe	0.29	0.08 – 1.12	0.07
Critical	0.02	0.01 – 0.10	$p < 0.001$
Age	0.96	0.92 – 0.99	0.014
Sex			
Male	0.40	0.13 – 1.24	0.11
Female	1		
Co-morbidity	0.64	0.43 – 0.96	0.03
Days since hospitalization	1.02	0.95 – 1.09	0.65
Supplemental Oxygen Requirement			
No requirement	1	0.10 – 1.11	0.07
Mild	0.34	0.03 – 0.38	$p < 0.01$
Moderate	0.10	0.01 – 0.08	$p < 0.001$
High	0.02		

AOR = Adjusted Odds Ratio; CI = Confidence Interval

RESULTS

80.4% of the patients in the sample were males. The average age of the patients was 54.5 years (SD = 14.5 years) and the average days since hospitalization for the patients were 8.65 (SD = 5.60). 30.7% of the patients had mild condition at the time of hospitalizations, whereas 35% were in severe condition and another 13.9% in critical condition. 73.6% of the patients in the sample did not require ICU care and 82.5% did not require intubation. 34.3% of the patients reported no co-morbidity whereas 34.7% reported three or more co-morbidity.

51.1% of the sample did not require supplemental oxygen at presentation, 23.9% required mild levels of supplemental oxygen (1 – 5 Liters/min), 11.1% required moderate levels (6 – 15 Liters/min) and 13.9% required high levels of supplemental oxygen.

Of the 280 patients admitted due to COVID-19, 82.9% survived whereas 17.1% died.

The descriptive analysis of cross tabulation in Table 2 shows that as the age of patients and number of co-morbidities increased, the percentage of expiry increased, and the percentage of survival decreased. Furthermore, with worsening condition, percentage of patients who expired increased.

Alternately, Graph 1 shows that the percentage of patients who survived and successfully discharged decreased with worsened condition. Likewise, the percentage of patients who expired increased as the supplemental oxygen requirement at admission increased, and the percentage of survival decreased as supplemental oxygen requirement at admission increased, shown in Graph 2.

The results for supplemental oxygen requirement show that the odds of survival were 0.10 times less in patients who required moderate levels of supplemental oxygen at presentation as compared to the patients who did not require supplemental oxygen (AOR = 0.10; 95% CI: 0.03 – 0.38). Likewise, the odds of survival were 0.02 times less in patients who required high levels (> 15 Litres/min) of supplemental oxygen as compared to the patients who did not require supplemental oxygen during the treatment (AOR = 0.02; 95% CI: 0.01 – 0.08).

Graph 3 shows patients requiring higher levels of supplemental oxygen were hospitalized for more days. The results of bivariate logistic analysis (see Table 4) show that the odds of discharge decreased in patients as the age increased (AOR = 0.96; 95% CI: 0.93 – 0.99). The odds of survival were 0.02 times less in patients who were critical at the time of admission as compared to patients whose condition were mild at the time of admission (AOR = 0.02; 95% CI: 0.01 – 0.10).

Table 3 also shows that as the number of co-morbidity increases, the odds of survival are decreased by 0.64 times (95% CI: 0.43–0.96; p<0.05).

DISCUSSION

This study is aimed at discussing the variable risk factors affecting the morbidity and mortality of patients suffering from Covid-19 focusing on hypoxemia at presentation leading to supplemental oxygen requirement, age, gender, and no. of already diagnosed co-morbidities. Some of these are non-modifiable however supplemental oxygen requirement due to hypoxemia at the time of admission to hospital is manageable and therefore preponement of admission to hospital for symptomatic patients carries significant importance in slowing down the progression of disease.[1]

Covid-19 causes variety of symptoms which could broadly be sequenced as starting from those of upper respiratory tract infection and later on to those of lower respiratory tract infection. With disease progression, a specific immune response is seen that cause atypical pneumonia due to cytokine storm The pulmonary infiltration due to cytokine storm not only exhibits as a problem itself but also predisposes to superimposed bacterial infections[11,12], cellular hypoxic injury, lactic acidosis, and eventually irreversible cell death. Therefore, most fruitful methodology of treatment involves early admission of symptomatic patients to hospital as soon as home monitoring of oxygen saturation shows a reading of 92% or lower at any point of time.

The phenomenon of "happy hypoxia" makes it difficult to rely the decision of admission to hospital on shortness of breath therefore oxygen saturation monitoring by a portable oximeter presents as a better indicator.[13,14]

In this study, at the time of admission 30.7% individuals had mild symptoms whereas 13.9% were critically ill. Out of total admissions, 26.4% required ICU care however metanalysis needs to be done to establish a link between various factors causing need for ICU care.

A trend observed in this study shows males being more affected with severe disease and had mortality of 18.7 percent of total male admissions as compared to that of females where only 10.9% expired. Also, significant direct relationship of age with morbidity and mortality is supported with 'p value' of 0.001 for all the patients. A retrospective cohort study done by Mayo Clinic on 140 patients suffering from Covid-19 reiterates the direct relationship between hypoxemia leading to higher supplementation and mortality and the role of increasing age. The older males were said to be the most affected subset.[15,7]

A study done by Journal of Molecular and Cellular Cardiology showed a higher case fatality with increasing age due to more significant effect produced on cardiomyocytes by SARS-CoV-2 in older patients.[16,17]

The no. of co-morbidities has direct relationship with disease severity as seen in this research having highly supportive 'p value' of 0.001. A cross-sectional study on over 16,000 hospitalized patients in UK also concludes that older age and male gender pose a higher risk for morbidity and mortality among Covid-19 patients among other factor including co-morbidities and unhealthy lifestyle including obesity and smoking.[18]

Although in this study, age and no. of co-morbidities are also seen to have a direct yet important role in determining the morbidity and mortality in Covid-19 patients, however, their meta-analysis is yet to be done with hypoxemia/supplemental oxygen requirement at presentation to determine the more accurate co-relation. Therefore, these factors will be discussed in detail in subsequent papers on the same set of data.

CONCLUSION

Among other factors, the supplemental oxygen requirement at the time of admission to hospital is one of the major determinants of prognosis among symptomatic covid-19 patients. Therefore, timely admission to hospital and prompt treatment could help in further reducing the mortality rate. However, follow up researches and meta-analysis should be done in this regard for better assessment.

Limitations of the Study

The results of this research need to be assessed with prudence as multiple parameters seem to affect the prognosis of critically ill patients hence meta-analysis needs to be done to be able to reach coherent results. Also, parallel studies should be done at other centers as well to widen the scope of supplemental oxygen requirement at presentation to hospital in prognosis projection.

Acknowledgments

This study was performed at Farooq Hospital West Wood Branch Lahore. We are thankful to all the patients for being a source of great learning and helping us in improving our management for future. We are also thankful to Mr. Jawad for statistical analysis of such an extensive data.

REFERENCES

1- Sun Q, Qiu H, Huang M, Yang Y. Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province. Annals of intensive care. 2020 Dec;10(1):1-4.

2- Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MM, Spijker R, Hooft L, Emperador D, Dittrich S, Domen J. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. Cochrane Database of Systematic Reviews. 2020(7).

3- Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, Li P, Hu B, Wang J, Hu C, Jin Y. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. The American journal of gastroenterology. 2020 May 1;115.

4- Goh KJ, Kalimuddin S, Chan KS. Rapid Progression to Acute Respiratory Distress Syndrome: Review of Current Understanding of Critical Illness from Coronavirus Disease 2019 (COVID-19) Infection. Ann Acad Med Singapore. 2020 Mar 1;49:108-8.

5- Dreher M, Kersten A, Bickenbach J, Balfanz P, Hartmann B, Cornelissen C, Daher A, Stöhr R, Kleines M, Lemmen SW, Brokmann JC. The characteristics of 50 hospitalized COVID-19 patients with and without ARDS. Deutsches Ärzteblatt International. 2020 Mar;117(10):271.

6- Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, Southern WN, Mantzoros CS. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism. 2020 Jul;108:154262.

7- Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, Liu S, Yang JK. Gender differences in patients with COVID-19: Focus on severity and mortality. Frontiers in Public Health. 2020 Apr 29;8:152.

8- Chen J, Qi T, Liu L, Ling Y, Qian Z, Li T, Li F, Xu Q, Zhang Y, Xu S, Song Z. Clinical progression of patients with COVID-19 in Shanghai, China. Journal of Infection. 2020 Mar 19.

9- Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet respiratory medicine. 2020 Apr 1;8(4):420-2.

10- Acosta MA, Singer BD. Pathogenesis of COVID-19-induced ARDS: implications for an aging population. European Respiratory Journal. 2020 Jan 1.

11- Jose M, Desai K. Fatal superimposed bacterial sepsis in a healthy Coronavirus (COVID-19) patient. Cureus. 2020 May;12(5).

12- Cox MJ, Loman N, Bogaert D, O'grady J. Co-infections: potentially lethal and unexplored in COVID-19. The Lancet Microbe. 2020 May 1;1(1):e11.

13- Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of 'happy' hypoxemia in COVID-19. Respiratory Research. 2020 Dec;21(1):1-9.

14- Tobin MJ, Laghi F, Jubran A. Why COVID-19 silent hypoxemia is baffling to physicians. American Journal of Respiratory and Critical Care Medicine. 2020 Aug 1;202(3):356-60.

15- Xie J, Covassin N, Fan Z, Singh P, Gao W, Li G, Kara T, Somers VK. Association between hypoxemia and mortality in patients with COVID-19. InMayo Clinic Proceedings 2020 Apr 11. Elsevier.

16- Robinson EL, Alkass K, Bergmann O, Maguire JJ, Roderick HL, Davenport AP. Genes encoding ACE2, TMPRSS2 and related proteins mediating SARS-CoV-2 viral entry are upregulated with age in human cardiomyocytes. Journal of Molecular and Cellular Cardiology. 2020 Jan 1.

17- Bansal M. Cardiovascular disease and COVID-19. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020 Mar 25.

18- Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020 Aug;584(7821):430-6.

IMPROVEMENT IN RENAL FUNCTION OF THE KIDNEY AFTER ANDERSON HYNES DISMEMBERED PYELOPLASTY

Manzoor Ahmed Malik,[1] Hassan Raza Asghar,[2] Waleed Miqal,[3] Malik Tahir Mehmood,[4] Mahboob Alam Chishti,[5] H M Amjad[6]

How to cite: Malik MA, Asghar HR, Miqal W, Mehmood TM, Chisti MA, Amjad HM. Improvement in renal function of the kidney after Anderson Hynes dismembered pylopasty. JAIMC. 2021; 19(1): 75-80.

Abstract

Objective: To assess the improvement in Renal Function, up to eight months after Anderson Hynes pyeloplasty in a previously obstructed kidney due to congenital pelvi ureteric junction obstruction. The study was conducted at Avicenna Medical College and Hospital Lahore

Methodology: Retrospective data analysis of 30 patients (20 boys, 10 girls) was done that presented to the Urology department from May 2016 to November 2019 with unilateral pelvi ureteric junction obstruction. We reviewed the records of 30 children who underwent dismembered pyeloplasty for unilateral ureteropelvic junction obstruction with no other associated urological abnormality. The follow-up duration was upto 8 months for all patients. Pre- and postoperative evaluation included technetium-99m dimercaptosuccinic acid (99mTc-DMSA) renal scan, technetium-99m diethylenetriaminepentaacetic acid (99mTc-DTPA) diuretic renography, and ultrasonographic examination. According to postoperative renal drainage halftime on diuretic renography, patients were divided into 2 groups: group A with normal renal drainage and group B with prolonged renal drainage for evaluation of their renal functional status.

Results: Postoperative diuretic renography revealed normal drainage (group A) in 54% of patients and prolonged drainage (group B) in 46%. The anteroposterior diameter (APD) of the renal pelvis of all patients showed improvement after pyeloplasty. There was no significant difference in improvement of the renal pelvic APD between the 2 groups. Furthermore, 92% of group A and 91% of group B had improved differential renal function (DRF) postoperatively.

Conclusions: Drainage half-time is not a reliable parameter for diagnosing obstructed hydronephrosis after pediatric pyeloplasty. We suggest that the renal pelvic APD and DRF should be considered when postoperative obstructed hydronephrosis is diagnosed using the criterion of prolonged renal drainage half-time on diuretic renography. Almost 90% of patients had Improvement in differential renal function following pyeloplasty.

Key Words: hydronephrosis, pyeloplasty, diuretic renography

Dismembered Anderson-Hynes pyeloplasty is a standard surgical treatment for ureteropelvic junction obstruction (UPJO). Successful pyeloplasty relieves symptoms and improves renal drainage, but the functional outcome after pyeloplasty continues to be debated because not all kidneys show improvement after surgery. In addition, there is considerable controversy in the literature on the final functional outcome and the factors influencing functional improvement after pyeloplasty. (1-renal function deterioration may be detected by a decrease in differential renal function (DRF) on technetium-99m dimercaptosuccinic acid (99mTc-DMSA) renal cortical scan or as an increase in renal pelvic size. Obstructed hydronephrosis is usually diagnosed by prolonged drainage half-time on technetium-99m diethylenetriaminepentaacetic acid (99mTc-DTPA) diuretic renography. However, Amarante et al.

1. Manzoor Ahmed Malik
2. Hassan Raza Asghar
3. Waleed Miqal
4. Malik Tahir Mehmood
5. Mahboob Alam Chishti
6. H M Amjad

1-5: Deptt of Urology Avicenna Medical College and Hospital Lahore
6. Department of Surgery, Sahiwal Medical College, Sahiwal

Correspondence:
Dr. Hassan Raza Asghar, Email; Hassanraza138@yahoo.com

Submission Date: 18-11-2020
1st Revision Date: 05-12-2020
Acceptance Date: 12-12-2020

reported that impaired renal drainage on diuretic renography using half-time should not be used as a sign of obstruction in children with unilateral renal pelvic dilatation.[4] According to recent studies, neither the degree of pelvic dilatation on ultrasonography nor obstruction on diuretic renography is a reliable indicator for surgery.[5,6] As surgeons, our major concern is to postoperatively recognize when the kidney remains truly obstructed after pyeloplasty. In order to detect true obstruction after pyeloplasty, we reviewed and analyzed data derived from preoperative and post-operative results from standardized diuretic renography, cortical renal scan, and ultrasonography. We examined the reliability of diuretic renography in diagnosing obstructive hydronephrosis after pyeloplasty and to assess the functional improvement after pyeloplasty.

METHODOLOGY

We retrospectively reviewed the records of 30 children who underwent dismembered pyeloplasty for unilateral UPJO. Patients with bilateral disease, associated vesicoureteral reflux, or significant postoperative complications requiring reintervention were excluded from this study. The surgical indications were based on progressive enlargement of hydronephrosis, prolonged renal drainage, and deteriorating renal function. Standard Anderson-Hynes pyeloplasties with internal ureteral stent placement were performed by the same surgeon between May 2016 to November 2019. Patient's ages ranged from 10 months to 10 years. Follow-up was upto 8 months for all patients. All patients were evaluated preoperatively with renal ultrasonography and 99m TcDTPA diuretic renography to confirm obstructed hydronephrosis. A 99mTc-DMSA renal cortical scan was also performed to assess DRF and the severity of cortical damage. Ultrasonography was undertaken during the initial examination and was repeated every 3 to 6 months after surgery. The degree of hydronephrosis was graded according to the Society of Fetal Urology (SFU) grading system, and the anteroposterior diameter (APD) of the renal pelvis was also recorded.[7] Follow-up 99mTc DMSA renal scan and 99mTc DTPA diuretic renography were obtained at 6 to 8 months. The renal cortical scan was performed 3 hours after intravenous injection of 148-259 MBq (4-7 mCi) of 99mTc DMSA. Five hundred thousand counts of anterior, posterior, and bilateral posterior oblique views were obtained with a 128Ű128 matrix size. The 99mTc DMSA relative differential renal cortical functions of the right and left kidneys were calculated with background subtraction of the geometric mean. An absolute increase in DRF of more than 5% in the operated kidney was considered significant.[8,9] A change in DRF of withinŲ 5% of the preoperative level was defined as stable renal function. The severity of cortical damage on the 99mTc DMSA renal scan was classified and scored according to a cortical damage scoring system based on previous literature.[10] The cortical damage scores included 1 for normal with no cortical damage, 2 for mild with focal cortical damage, 3 for moderate with more general damage and greater kidney length, and 4 for severe mixing with global cortical damage with the possible inclusion of a small segment of the normal cortex. For diuretic renography, all patients were advised to drink 300 ml of water 30 min before the diuretic study to ensure adequate hydration. Imaging was performed in the supine position with the scintillation camera below the table. Data were acquired at 15-s intervals with a 15-s 64Ű64 matrix size. Up to 40 mg (1 mg/kg) of furosemide was injected intravenously at 20 min after injection of 185-296 MBq (5-8 mCi) of 99mTc-DTPA. Patients were asked to stand up and empty their bladders before the furosemide injection. Clearance half-time of the radioactive urine from each side of the renal pelvis was calculated with background subtraction by exponential curve fitting after the furosemide injection.[11] Clearance half-time of less than 20 min on DTPA diuretic renography was interpreted as normal renal drainage. Prolonged renal drainage was defined as a half-time of greater than 20 min.[12] Patients were then divided into 2 groups: group A with normal renal drainage and group B with prolonged renal drainage.

Ultrasonographic findings, renal pelvic APD, hydronephrosis grade, DRF, and cortical dam-age score were compared between the 2 groups. Data were analyzed using unpaired Student's t-test, and a p value of < 0.05 was considered significant.

RESULTS

From May 2016 to November 2019, a total of 30 children (20 boys and 10 girls) underwent dismembered pyeloplasty at Avicenna medical and dental college Lahore. Six patients were excluded due to loss of follow-up and/or missing renal scans. Of the remaining 24 patients, 18 underwent right-side and 6 underwent left-side pyeloplasties. The mean patient age at time of surgery was 5.2 (range, 0.8-10) years. The mean follow-up was 5.8 (range, 4.2-8) months. All reconstructed kidneys demonstrated decreased hydronephrosis on follow-up ultrasonography. On average, the renal pelvic APD had decreased by over 57% of the initial APD of the renal pelvis by 6 months after surgery. Diuretic renography at 5 to 8 months after surgery showed normal renal drainage in 13 patients (54%) and prolonged renal drainage in 11 patients (46%). In accordance with the SFU hydronephrosis grade, most patients had grade 3 (7 patients) or grade 4 (17 patients) hydronephrosis on preoperative ultrasonography. Similarly, preoperative 99mTc-DMSA renal scans revealed moderate or severe cortical damage in 21 cases (88%) (Table1).

Table 1:

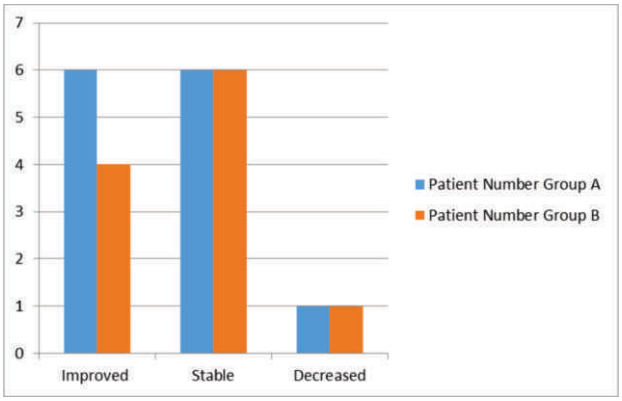
	Renal Drainage Normal	Renal Drainage Prolonged
Number of Patients	13	11
Number on Left side	11	9
Number on Right side	2	2
Number with a Hydronephrosis grade of 3	2	3
Number with a Hydronephrosis grade of 4	11	8
Number with a Cortical Damage Score of 2 (Mild)	3	0
Number with a Cortical Damage Score of 3 (Moderate)	4	6
Number with a Cortical Damage Score of 4 (Severe)	6	5

Follow-up ultrasonography showed decreased hydronephrosis in both the prolonged and normal renal drainage groups. All 11 patients with prolonged renal drainage were monitored for 8 months, and none of them was subsequently diagnosed with symptomatic recurrence (flank pain, urinary tract infection, hematuria, or renal calculi). Furthermore, the DRF of the 11 reconstructed kidneys with prolonged drainage was revealed to be stable in 6 cases, improved in 4, and decreased in 1 (Fig. 1). There were no statistically significant differences ($p > 0.05$, by unpaired t test) in age at surgery, initial renal pelvic APD, initial DRF, initial cortical damage score, or improvement in renal pelvic APD between the 2 groups (Table 2).

Table 2:

Parameters	Normal	Renal Drainage Prolonged	P
Number of Patients	13	11	
age at surgery (years)	4.6±3.3	5.8±3.3	0.24
initial renal pelvic APD (cm)	4.6±0.5	5.3±1.8	0.22
initial DRF (%)	44.7±11.4	35.2±14.6	0.1
initial cortical damage score	3.2±0.8	3.4±0.5	0.28
improbement in renal pelvic APD (%)	68.2±14.6	56.7±19.0	$^{0.1}$

The small sample size is a possible reason for the lack of statistical significance. Postoperatively, DRF improved in 10 patients (42%), remained stable in 12(50%), and deteriorated in only 2(8%). Actually, 1 of the 2 patients with deteriorated renal function had a normal drainage half-time. Thus, the kidney with unimproved renal function did not correlate with poor drainage in our series. Overall, 92% of patients, who included those with improved or stable renal function, had good DRF after surgery. The degree of DRF improvement ranged from 5.2% to 12.8% (mean ŲSD, 10.2%Ų2.7%). A high proportion of patients with improved or stable DRF was found not only in group A (12/13, 92%) but also in group B (10/11, 91%) (Fig. 1). Moreover, none of the children required further surgery for recurrent obstruction during the follow-up period.



DISCUSSION

Several reports have advocated early relief of UPJO to allow function to recover or to prevent further loss of kidney function.[5,13] Some studies have suggested that affected kidneys with good DRF at the time of diagnosis are less likely to manifest deterioration of renal function after surgery.[3] In contrast, other series concluded that renal function did not improve after pyeloplasty, regardless of the initial level of renal function.[2] Salem et al. also observed that only kidneys with impaired preoperative function were associated with greater degrees of improvement after surgery.[9] In the study by Zaccara et al., an increase or decrease in renal function was found to be randomly distributed among patients operated upon at different ages, and the unpredictability of postoperative renal function was also emphasized.[14] Likewise, in our study, neither initial renal pelvic APD nor preoperative DRF could be used to predict which obstructed kidneys would benefit from surgery. On the other hand, diuretic renography has been widely used to differentiate true obstructed hydronephrosis. However, some authors have questioned the interpretation of the obstructive patterns of diuretic renography and drainage half-times for the diagnosis of hydronephrosis.[15,16] The definition of obstruction based on a 20-min washout after the diuretic challenge is useful in symptomatic older children and adults, but assuming that the same criteria can be used in an asymptomatic group of young children has gene-rated debate.[4,15,16] Therefore, some controversy has arisen concerning children with unilateral renal pelvic dilatation diagnosed by diuretic renography. One issue is the variable drainage halftime on follow-up diuretic renography, and second is the concern over interpretation of results of diuretic renography showing impaired drainage. Many insti-tutions have reported inadequate responses to the diuretic challenge without incorporating the impor-tant factors of an empty bladder and gravity drainage in acquiring and analyzing the data.[4,17,18] It was assumed that progressive renal deterioration had begun only when there was a decrease in renal function and/or progressive dilatation of the renal pelvis. Thus, we analyzed the group of 11 patients (46%) with prolonged renal drainage despite stable renal pelvis dilatation on ultrasonography in order to determine an underlying cause for the prolonged drainage. According to our results, DRF was stable in 6 patients, increased in 4, and decreased in 1. In fact, the patient who presented with a postoperative decrease in DRF had a preoperative renal scan showing supra-normal renal function (SNRF) with renal function up to 77%. The problem of SNRF has previously been encountered and reported in the literature.[19] At present, the phenomenon is not well understood. Although this patient had, according to our definition, deteriorating renal function after surgery in comparison to preoperative values, the DRF had nearly returned to normal compared to the contralateral kidney. Therefore, this patient should not have been assigned to the group with decreased DRF, upon consideration of these data. In other words, all 11 patients had improved or stable DRF postoperatively. All of the children who presented with prolonged renal drainage revealed remarkable decreases in renal pelvic APD of greater than 57%, compared to their initial ultrasonographic findings. We observed that all of the children in our study had stable hydronephrosis for at least a 8 months follow-up period with respect to pelvic size on ultrasonography and DRF on renal cortical scan. Stable hydronephrosis was considered to provide reassurance that the ureteropelvic junction remained patent

unless symptoms persisted. Thus, those kidneys with prolonged drainage were considered not to have obstructed hydronephrosis. None of those children underwent surgery for recurrent obstruction during the more than 5-year follow-up period. The 11 children, with persistently impaired drainage on all of their follow-up diuretic renographies, preserved these DRFs and had stable renal pelvic sizes, representing important evidence that observations based simply upon impaired drainage may be inadequate for diagnosing postoperative obstruction. Appropriately interpreting drainage half-time is a difficult task. The wide interpatient and intrapatient variability of renal drainage on renography may indicate that the current methods of characterizing drainage are not sufficiently reliable or sensitive parameters for diagnosing obstruction. One study, which was similar to our investigation, reported that prolonged drainage half-time and/or high-grade hydronephrosis is an indicator neither of renal obstruction nor for surgery.[20] When diuretic renography is performed, the importance of allowing the bladder to empty as well as having the patient in an erect posture has previously been described.[12,16] Improvement in renal drainage half-time after voiding and changing gravity while the patient is standing has been reported.[4,16] From our experience, drainage half-time derived from traditional diuretic renography is not a reliable factor but a relative reference. Accordingly, impaired renal drainage, in the absence of concurrent data on renal function or ultrasonography, does not appear to justify conclusion a diagnosis of obstruction. In conclusion, diagnosis of obstructed hydronephrosis cannot simply be based on prolonged renal drainage in patients with stable and asymptomatic postoperative hydronephrosis. We recommend that the renal pelvic anteroposterior diameter on ultrasonography and differential renal function on 99mTc DMSA should be taken into account when obstructed hydronephrosis is diagnosed using the criterion of prolonged drainage on 99mTc-DTPA diuretic renography.

REFERENCES

1. MacNeily AE, Maizels M, Kaplan WE, Firlit CF, Conway JJ. Does early pyeloplasty really avert loss of renal function? A retrospective review. J Urol 1993;150:769-73.
2. McAleer IM, Kaplan GW. Renal function before and after pyeloplasty: does it improve? J Urol 1999; 162:1041-4.
3. Chertin B, Fridmans A, Knizhnik M, Hadas-Halperin I, Hain D, Farkas A. Does early detection of ureteropelvic junction obstruction improve surgical outcome in terms of renal function? J Urol 1999;162(3 Pt 2):1037-40.
4. Amarante J, Anderson PJ, Gordon I. Impaired drainage on diuretic renography using half-time or pelvic excretion efficiency is not a sign of obstruction in children with a prenatal diagnosis of unilateral renal pelvic dilatation. J Urol 2003;169:1828-31.
5. Palmer LS, Maizels M, Cartwright PC, Fernbach SK, Conway JJ. Surgery versus observation for managing obstructive grade 3 to 4 unilateral hydronephrosis: a report from the Society for Fetal Urology. J Urol 1998; 159:222-8.
6. Subramaniam R, Kouricfs C, Dickson AP. Antenatally detected pelvi-ureteric junction obstruction: concerns about conservative management. BJU Int 1999;84:335-8.
7. Fernbach SK, Maizels M, Conway JJ. Ultrasound grading of hydronephrosis: introduction to the system used by the society for fetal urology. Pediatr Radiol 1993;23:478-80.
8. Capolicchio G, Leonard MP, Wong C, Jednak R, Brzezinski A, Salle JL. Prenatal diagnosis of hydronephrosis: impact on renal function and its recovery after pyeloplasty. J Urol 1999;162(3 Pt 2): 1029-32.
9. Salem YH, Majd M, Rushton G, Belman AB. Outco 349 analysis of pediatric pyeloplasty as a function of patient age, presentation and differential renal function. J Urol 1995;154:1889-93.
10. Konda R, Sakai K, Ota S, Abe Y, Hatakeyama T, Orikasa S. Ultrasound grade of hydronephrosis and severity of renal cortical damage on 99mtechnetium dimercaptosuccinic acid renal scan in infants with unilateral hydronephrosis during followup and after pyeloplasty. J Urol 2002;167:2159-63.
11. Kao PF, Sheih CP, Tsui KH, Tsai MF, Tzen KY. The 99mTc-DMSA renal scan and 99mTc-DTPA diuretic renogram in children and adolescents with incidental diagnosis of horseshoe kidney. Nucl Med Commum 2003; 24:525-30.

12. Gordon I, Colarinha P, Fettich J, Fischer S, Frokier J, Hahn K, Kabasakal L, Mitjavila M, Olivier P, Piepsz A, U P, Sixt R, van Velzen J. Guidelines for standard and diuretic renography in children. Eur J Nucl Med 2001;28: BP21-30.
13. DiSandro MJ, Kogan BA. Neonatal management. Role for early intervention. Urol Clin North Am 1998;25:187- 97.
14. Zaccara A, Marchetti P, Sala El, Caione P, De Gennaro M. Are preoperative parameters of unilateral pyelo-ureteric junction obstruction in children predictive of postoperative function improvement? Scand J Urol Nephrol 2000; 34:165-8.
15. Gordon I. Diuretic renography in infants with prenatal unilateral hydronephrosis: an explanation for the controversy about poor drainage. BJU Int 2001;87:551-5.
16. Reilly PH, Aurell M, Britton K, Kletter K, Rosenthal L, Testa HJ. Consensus on diuresis renography for investigating the dilated upper urinary tract. Radionuclides in Nephrourology Group. Consensus Committee on Diuresis Renography. J Nucl Med 1996;37:1872-6.
17. Saunders CA, Choong KK, Larcos G, Farlow D, Gruenewald SM. Assessment of pediatric hydronephrosis using output efficiency. J Nucl Med 1997; 38:1483-6.
18. Rossleigh MA, Leighton DM, Farnsworth RH. Diuresis renography. The need for an additional view after gravityassisted drainage. Clinl Nucl Med 1993;18:210-3.
19. Houben CH, Wischermann A, Borner G, Slany E. Outcome analysis of pyeloplasty in infants. Pediatr Surg Int 2000;16:189-93.
20. Ulman I, Jayanthi VR, Koff SA. The long-term followup of newborns with severe unilateral hydronephrosis initially treated nonoperatively. J Urol 2000;164:1101-5.

KNOWLEDGE, AWARENESS AND PRACTICES TOWARDS ANNUAL INFLUENZA VACCINATION AMONG HEALTH CARE PROVIDERS IN JINNAH HOSPITAL, LAHORE

Fatima Khalid,[1] Fizza Maheen,[2] Mahdin Gulzar,[3] Fatima Ahmad,[4] Moeed Ahmad[5]

How to cite: Khalid F, Maheen F, Gulzar M, Ahmad F, Ahmad M. Knowledge, awareness and practices towards annual influenza vaccination among health care providers in Jinnah Hospital Lahore. JAIMC. 2021; 19(1): 81-86.

Abstract

Background: The rising cases of influenza and threats of epidemics formed the driving force for this study, which aims to investigate the status of awareness and vaccination of influenza among Health Care Providers (HCPs).

Objective: This study intends to evaluate the practices and trends of influenza vaccination among HCPs along with the reasons for not getting vaccinated. It also asses the level of knowledge and awareness of HCPs regarding influenza and its vaccination.

Methodology: A pre-tested questionnaire was used for data collection, distributed to 250 HCPs, comprising of Registrars, Post Graduate Residents, House Officers and Paramedical Staff. . The data collected was entered and analyzed in SPSS v25.0.Mean and SD were calculated for variables such as age while frequencies and percentages were used for categorical variables.

Results: 54.7% HCPs were from 'Medicine and Allied', while 45.3% belonged to 'Surgery and Allied'. Only 30.5% HCPs were found to be vaccinated for influenza. 43.5% Paramedical Staff were vaccinated compared to 29.0% Doctors. More HCPs in 'Surgery & Allied' (35.5%) were found to be vaccinated than those in 'Medicine & Allied' (26.2%). (81.3%) HCPs in 'Medicine & Allied' received the vaccination "Annually" in comparison to the (0%) HCPsin 'Surgery & Allied'. 'Lack of Knowledge' (81.6%) was identified as the major barrier in influenza vaccination. 65.90% HCPs were evaluated to be 'Aware' of influenza vaccination.

Conclusion: The low annual immunization rates of HCPs calls for the mobilization of resources concerning awareness and practices. Enrollment of programs regarding flu vaccination at government level are necessary to increase vaccination levels and prevent influenza among HCPs.

Key Words: Awareness, healthcare providers, influenza, influenza vaccination, knowledge, medical doctors, paramedical staff, practices.

Following the scare of Influenza Pandemic, A/H1N1 in 2009; Influenza has been declared a seasonal flu virus that continues to cause significant morbidity and mortality on a yearly basis since 2010.[1] It alone causes 200,000 hospitalizations on annual basis.[2] There were a minimum of 35 deaths in Eastern Punjab region reported by medical off-icers in January 2019.[3] The surge of influenza cases throughout Pakistan has given rise to a concern regarding measures that can be employed to prevent the disease.[4] Vaccination is the most appropriate solution.[5] In fact, the generation of herd immunity; by maximizing seasonal influenza vaccination has been declared the best way to limit the spread of this highly contagious disease.[6]

Influenza; also known as Flu is transmitted by respiratory droplets. Antigenic shift and drift necessitates the yearly vaccination which is formulated twice a year. WHO and NIH have issued guidelines

1. Fatima Khalid
2. Fizza Maheen
3. Mahdin Gulzar
4. Fatima Ahmad
5. Moeed Ahmad

1-5. Department of Community Medicine, Allama Iqbal Medical College, Lahore

Correspondence:
Dr. Fatima Khalid, E-mail: *Fatimakhalid04@gmail.com*

Submission Date: 11-11-2020
1st Revision Date: 29-11-2020
Acceptance Date: 03-12-2020

regarding annual influenza vaccination to prevent infection and severe outcomes; especially in high risk groups: pregnant women, children aged between 6 months to 5 years, elderly individuals (aged more than 65 years), individuals with chronic medical conditions and health-care workers (HCPs).[7,8] Generally, HCPs are more likely to be exposed to respiratory pathogens[9] Influenza virus is widely distributed. Even then most of the HCPs are not vaccinated against it; which can increase the risk of the virus infecting them and HCPs acting as carriers that transmit the virus across patients. In spite of the international efforts that are being made to minimize the damage being done by influenza through immunization, only 2(18%) of South East Asian countries have an influenza immunization policy.[10] Accor-ding to a study conducted among 300 HCPs, 38 (17.7%) doctors were reported to have received some kind of vaccination.[11] The rate of immuni-zation among HCPs in Pakistan is suboptimal.

Literature review reveals poor adherence of HCPs to influenza vaccination guidelines. One of the only two studies done among medical doctors at Tertiary Health Care Settings in Peshawar, attributed lack of awareness, unavailability of vaccination, cost of vaccination and insufficient staff to the low coverage of influenza immunization in the HCPs of Pakistan.[11] The main reasons for vaccine acceptance among HCPs included self-protection and protection of family.[12] This study aims at analyzing the level of awareness and practice of influenza immunization among HCPs in one of the biggest medical institutes of Pakistan's major city – Lahore. The findings of this study will not only shed light on the need to implement constructive steps towards achieving a satisfactory threshold of immunization among HCPs but will also serve as the foundation for expansion of influenza immunization programs into a nation-wide campaign.

Primary Objective: Evaluate Influenza Vacci-nation Practices among HCPs;

a) Percentage of HCPs that are vaccinated against influenza at least once in their life
b) Trends of vaccination among HCPs
c) Reasons for not getting vaccinated

Secondary Objectives: Quantified assessment of Knowledge, awareness and practices about influenza.

METHODOLOGY

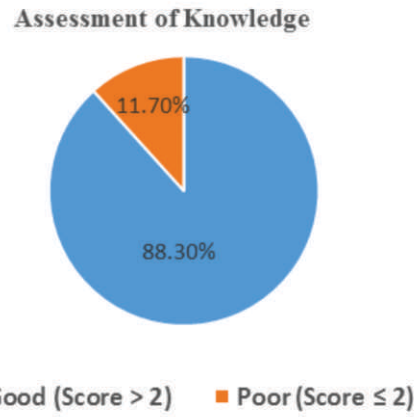
The sample size was calculated using open EPI Software at 95% confidence level taking frequency of anticipated factor (frequency of HCPs vaccinated against influenza) as 9% and margin of error as 5%. Sample size came out to be 119 but 250 participants were recruited, which fulfilled the inclusion criteria, among which 223 responded. Each participant gave written consent and completed a structured questionnaire. The data collected was entered and analyzed in SPSS v25.0. Mean and SD were calculated for variables such as age while frequencies and percentages were used for categorical variables. For the 4 items used to assess knowledge, scoring of the responses was done using 1 and 0 for correct and incorrect responses respectively. Cross tabulations of knowledge and awareness were made against Department and Designation. Moreover, the chi-squared test was applied to determine whether there is a significant difference between the expected frequencies and the observed frequencies in one or more categories. P-value of < 0.05 was set significant for all of the statistical tests.

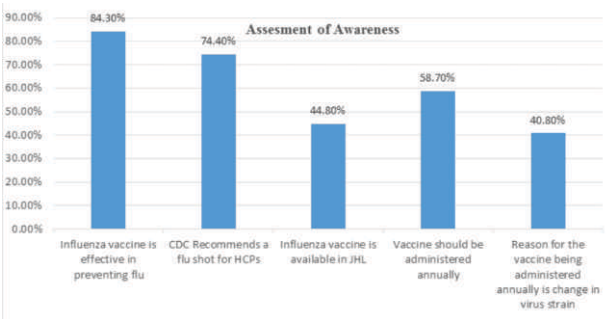
RESULTS

A total of 250 HCPs were invited and 223 took part in the study with a response rate of 89.2%. Mean age of the respondents was 27.24 ± 5.06 years with 51.1% female population. 54.7% HCPs were from Medicine and Allied Sciences, while 45.3% belonged to Surgery and Allied Sciences. By designation, maximum respondents were House Officers (54.7 %), followed by Post Graduate Trainees (22.4%), Paramedical Staff (10.3%), Medical Officers (8.5%) and Registrars (4%). An assessment of vaccination status found only 30.5% HCPs to be vaccinated for influenza. 13.90% respondents reported to have

been vaccinated annually. When a comparison was done to check vaccination status against designation; it was found that 43.5% Paramedical Staff was vaccinated while 29.0% Doctors were vaccinated for influenza. Vaccinated HCPs in 'Surgery & Allied Disciplines' (35.5%) were found to be more than those in 'Medicine & Allied Disciplines.' (26.2%) However, 81.3% HCPs in 'Medicine & Allied Disciplines' received the vaccination "Annually" in comparison to the 0% HCPs in 'Surgery & Allied Disciplines' – who primarily reported having received the vaccination "Once in a lifetime." A chi square test was performed that revealed that there was insignificant difference (0.129) between the vaccinated HCPs of 'Medicine & Allied' and 'Surgery & Allied'. On the contrary, there was significant difference (0.000) between the Annually vaccinated HCPs of 'Medicine & Allied' and 'Surgery & Allied'.

For knowledge of HCPs regarding influenza, 4 Questions were asked to assess the perception of people regarding influenza vaccination; a scoring scale was set. Those who gave 2 or less than two correct answers were labelled to have a "Poor knowledge" regarding influenza. Those who gave more than 2 correct answers were labelled to have a "Good knowledge" regarding Influenza. According to this scale, a good 88.3% of the respondents were found to have a sound understanding of the morbidity, spread and importance of influenza. Furthermore, a set of 5 Questions was asked to assess, in depth, the level of awareness of the respondents regarding the effectivity, recommendations, availability and regimen for influenza vaccination. A scoring scale was set; according to which those who opted for two or less than two correct answers were labelled "Unaware," while those who chose more than two correct options were labelled as being "Aware." It was found that 65.90% Health Care Provides were well aware while 34.10% were "Unaware."





DISCUSSION

Acknowledging the widespread prevalence of influenza virus in Pakistan and the importance of preventative medicine, this study was conducted to assess influenza vaccination status and trends among HCPs.[12] The importance of influenza vaccination in limiting the morbidity and mortality of influenza has already been established by several published studies and recognized by the WHO.[13,6,14]

This was a first of its kind study to be held in

Table 1:

Vaccine status	Response	Medicine and Allied	Surgery and Allied	Chi-square P value
Have you ever had a flu vaccination?	Yes	32 (26.2%)	36 (35.5%)	$X^2 = 2.310$ P = 0.129
How often do you get vaccinated for influenza?	Annually	26 (81.3%)	0 (0.0%)	
	Every six months	5 (15.6%)	0 (0.0%)	$X^2 = 64.095$
	Once in a lifetime	1 (3.1%)	36 (100.0%)	P = 0.000

Jinnah Hospital Lahore. In comparison to similar studies reported in our country, our study was conducted in a much larger Tertiary Health Care setting, included all HCPs and involved detailed analysis of trends of vaccination. In our study we found out that in spite of repeated CDC and ACIP recommendations, the rates of vaccinated HCPs in one of the biggest THC settings of Pakistan – Jinnah Hospital Lahore – were found to be 30.5% This, when compared with the results of a previous studies: Srinagar India (4.4%), Sierra Leone(6.5%), Turkey (26.7%), Italy (36 %), seems like a breakthrough.[15,16,17,18] Moreover, we found our study to exhibit a greater number of immunized Doctors (29.0%) than a prior study in Peshawar, Pakistan (8.84%).[10] However, the fact that 84.30% HCPs were aware of the effectiveness of influenza vaccination, yet did not practice the immunization.

Another finding of our study was that even though 58.7% of our respondents were aware that the vaccine was to be administered annually, only 13.9% actually put this to practice. Similar findings were reported from other studies.[16,21]

In contrast to all previous studies, our study analyzed and cross tabulated the various factors that affected influenza immunization among HCPs on a much deeper level. Doctors were found to be less vaccinated (29.0%) than Paramedical Staff (43.5%). This was in contrast with prior studies that revealed chances of Physicians being immunized were much greater than chances of nurses being immunized.[19,17,20] This is probably because the Paramedical Staff in Jinnah Hospital receives special training regarding the importance of receiving immunization on a regular basis. This is a major breakthrough since Paramedical Staff has closer, more frequent contact with patients than Doctors and an increase in their vaccination rates correlates to decreased transmission of the virus.

In a deeper analysis, we were unable to find a positive correlation between Vaccination rates and Department to which the HCPs belonged. It was found that there was significant difference ($p < 0.05$) in the repetition of immunization among people from Medicine and Allied than Surgery and Allied. 81.6% of our respondents linked low influenza immunization rates to lack of knowledge. These findings are in agreement to the results reported in studies conducted earlier which attributed the knowledge gap and lack of awareness to low immunization rates[10,15,25]. Conversely, our study demonstrated that HCPs were knowledgeable about the infection and aware of the vaccination; and yet demonstrated low compliance rates to the vaccine. A cause of this could be the mere lack of enthusiasm among the HCPs to get vaccinated.

Our assessment of knowledge of respondents about influenza revealed that 88.3% HCPs were knowledgeable about Influenza which was analogous to the results of prior studies[15]. Nearly 96.9% of the doctors have a belief that Influenza is transmitted primarily by respiratory droplets (through coughing and sneezing); similar to another study conducted in Peshawar.[10,15]

The greater susceptibility of HCPs to influenza was known by 91.5% of our respondents; which is a big step forward from the 48.5% in an Italian study.[22] This can be attributed to the greater level of exposure with patients having influenza in tertiary care hospitals in our case setting.

In line with a previous study, Physicians were found to have maximal perception of influenza, followed by Paramedical staff.[15] Data concerning the level of awareness about influenza vaccination showed considerable variance. Accordingly, 74.40% were aware of the fact that CDC recommends influenza shots for HCP as compared to the 54.0% in a prior Peshawar study.[23] A meager 58.70% HCPs were familiar with annual requirement of vaccine with 40.80% claiming to have known the accurate reason for annual need. A study in Italy showed that majority of respondents disagreed that vaccine is effective (62.6%),[24] whereas, our study revealed that 84.3% HCPs were aware of influenza vaccine effectiveness; which is quite satisfactory. In spite of this, the awareness of the annual influenza vaccina-

tion lags far behind the awareness of vaccine efficacy. In order to overcome this incongruity, a detailed insight into guidelines published by CDC is required.

Limitations of Study

The population of respondents who were Physicians was much greater than the Paramedical Staff; which might have affected the individual cross tabulations of Designation with Practice of influenza immunization. Recall bias and response bias may have led to altered reporting of the practices of influenza vaccination. More Tertiary Health Care Hospitals could have been included in the research to get a generalized status of vaccination across Lahore.

CONCLUSION

Despite the fair knowledge of morbidity and mortality of influenza virus and its immunization amongst HCPs, a very low proportion was found to be adherent to the CDC vaccination guidelines. Lack of availability and cost of vaccine effect the compliance of HCPs to Influenza vaccination.

Recommendations

Multiple strategies need to be applied in order to not only rigorously remind HCPs of the need to get vaccinated, but also to ensure adherence to the annual requirement of the flu shot administration. There is a need for annual camps to ensure that the entire HCPs in hospitals are immunized. Government Health Authorities need to carry out regular surveillance of the status of vaccination in HCPs to keep a track record of the immunized individuals. Widespread awareness seminars should be held to educate the masses and remove their misconceptions. Evaluating carefree attitude of the HCPs as a major barrier to immunization, massive incentives to get vaccinated seems like the best option to motivate them.

Acknowledgments

To Dr. Sana Iftikhar and Dr. Mamoon A. Qureshi, we thank wholeheartedly for walking with us through every step of the research project. We also extend our gratitude to all the subjects of our research, without whom this would not have been possible.

Conflict of Interest: None

Funding Source: None

REFERENCES

[1] Qasim M. Influenza A H1N1 virus may cause localised outbreaks [Internet]. thenews. TheNews International; 2018 [cited 2019Jun1]. Available from: https://www.thenews.com.pk/print/412432-influenza-a-h1n1-virus-may-cause-localised-outbreaks

2. Santaularia J, Hou W, Perveen G, Welsh E, Faseru B. Prevalence of influenza vaccination and its association with health conditions and risk factors among Kansas adults in 2013: a cross-sectional study [Internet]. BMC public health. BioMed Central; 2016 [cited 2019Jun1]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26911615

3. Tribune.com.pk. Pakistan among countries battling record flu, face rising death tolls [Internet]. The Express Tribune. 2018 [cited 2019Jun3]. Available from: https://tribune.com.pk/story/1625567/3-pakistan-among-countries-battling-record-flu-face-rising-death-tolls/

4. Junaidi I. Flu virus outbreak may hit country, warns NIH [Internet]. DAWN.COM. 2018 [cited 2019 Jun 3]. Available from: https://www.dawn.com/news/1448513/flu-virus-outbreak-may-hit-country-warns-nih

5. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention; [cited 2019 Jun 3]. Available from: https://www.cdc.gov/flu/protect/ habits/index.htm

6. Influenza (Seasonal) [Internet]. World Health Organization. World Health Organization; [cited 2019 Jun3]. Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)

7. https://www.nih.org.pk/wp-content/uploads/ 2018/11/Advisory-H1N1-Nov-2018.pdf

8. Dini G, Toletone A, Sticchi L, Orsi A, Bragazzi NL, Durando P. Influenza vaccination in healthcare workers: A comprehensive critical appraisal of the literature [Internet]. Human vaccines & immunotherapeutics. Taylor & Francis; [cited 2019Jun1]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/ 28787234

9. A global review of national influenza immunization policies: Analysis of the 2014 WHO/UNICEF Joint

Reporting Form on immunization [Internet]. Vaccine. Elsevier; 2016 [cited 2019Jun3]. Available from: https://www.sciencedirect.com/science/article/ pii/S0264410X16306430

10. Ali I, Ijaz M, Rehman IU, Rahim A, Ata H. Knowledge, Attitude, Awareness, and Barriers Toward Influenza Vaccination Among Medical Doctors at Tertiary Care Health Settings in Peshawar, Pakistan-A Cross-Sectional Study [Internet]. Frontiers in public health. Frontiers Media S.A.; 2018 [cited 2019Jun1]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6030373/
11. Badar N, Aamir UB, Mehmood MR, Nisar N, Alam MM, Kazi BM, et al. Influenza Virus Surveillance in Pakistan during 2008-2011 [Internet]. PLOS ONE. Public Library of Science; [cited 2019Jun1]. Available from: https://journals.plos.org/ plosone/article?id=10.1371/journal.pone.0079959[13] Carman WF, Elder AG, Wallace LA, McAulay K, Walker A, Murray GD, et al. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial [Internet]. Lancet (London, England). U.S. National Library of Medicine; 2000 [cited 2019Jun1]. Available from:https://www.ncbi.nlm.nih.gov/pubmed/10675165
14. Ahmed, Faruque, Lindley, Allred, Norma, Weinbaum, et al. Effect of Influenza Vaccination of Healthcare Personnel on Morbidity and Mortality Among Patients: Systematic Review and Grading of Evidence [Internet]. OUP Academic. Oxford University Press; 2013 [cited 2019Jun3]. Available from: https://academic.oup.com/cid/article/58/1/50/ 372080
15. James PB, Rehman IU, Bah AJ, Lahai M, Cole CP, Khan TM. An assessment of healthcare professionals' knowledge about and attitude towards influenza vaccination in Freetown Sierra Leone: a cross-sectional study [Internet]. BMC public health. BioMed Central; 2017 [cited 2019Jun3]. Available from:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5584505/
16. Çiftci F, Şen E, Demir N, Çiftci O, Erol S, Kayacan O. Beliefs, attitudes, and activities of healthcare personnel about influenza and pneumococcal vaccines [Internet]. Human vaccines & immunotherapeutics. Taylor & Francis; [cited 2019Jun3]. Available from: https://www.ncbi.nlm.nih.gov/pmc/ articles/PMC5791560/#__ffn_sectitle
17. Vanessa Cozza, Valeria Alfonsi, Maria Cristina Rota, Valerio Paolini, AttiMLCdegli. Promotion of influenza vaccination among HCP: findings from a tertiary care children's hospital in Italy [Internet]. BMC Public Health. BioMed Central; 2015 [cited 2019Jun3]. Available from: https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-015-2067-9
18. Bali NK, Ashraf M, Ahmad F, Khan UH, Widdowson M-A, Lal RB, et al. Knowledge, attitude, and practices about the seasonal influenza vaccination among healthcare workers in Srinagar, India [Internet]. Influenza and other respiratory viruses. Blackwell Publishing Ltd; 2013 [cited 2019Jun3]. Available from: https:// www. ncbi. nlm. nih. gov/ pubmed/ 22862774/
19. Zhang J, While AE, Norman IJ. Knowledge and attitudes regarding influenza vaccination amongnurses: A research review. Vaccine. 2010; 28(44): 7207–14.https://www.researchgate.net/ publication/46094770_Knowledge_and_attitudes_regarding_influenza_vaccination_among_nurses_A_research_review
20. Riphagen-Dalhuisen J, Gefenaite G, Hak E. Predictors of seasonal influenza vaccination among healthcare workers in hospitals: a descriptive meta-analysis [Internet]. Occupational & Environmental Medicine. BMJ Publishing Group Ltd; 2012 [cited 2019Jun3]. Available from: https:// oem. bmj. com/content/69/4/230.full
21. Asma S, Akan H, Uysal Y, Poçan AG, Sucaklı MH, Yengil E, et al. Factors effecting influenza vaccination uptake among HCP: a multi-center cross-sectional study [Internet]. BMC infectious diseases. BioMed Central; 2016 [cited 2019Jun3]. Available from:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4855819/?report=reader#__ffn_sectitle
22. Durando P, Alicino C, Dini G, Barberis I, Bagnasco AM, Iudici R, et al. Determinants of adherence to seasonal influenza vaccination among healthcare workers from an Italian region: results from a cross-sectional study [Internet]. BMJ open. BMJ Publishing Group; 2016 [cited 2019Jun3]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4874132/#!po=36.9565
23. Ali I, Ijaz M, Rehman IU, Rahim A, Ata H. Knowledge, Attitude, Awareness, and Barriers Toward Influenza Vaccination Among Medical Doctors at Tertiary Care Health Settings in Peshawar, Pakistan-A Cross-Sectional Study [Internet]. Frontiers in public health. Frontiers Media S.A.; 2018 [cited 2019Jun3]. Available from: https://www.ncbi.nlm.nih.gov/ pmc/articles/PMC6030373/#!po=70.0000
24. Durando P, Alicino C, Dini G, Barberis I, Bagnasco AM, Iudici R, et al. Determinants of adherence to seasonal influenza vaccination among healthcare workers from an Italian region: results from a cross-sectional study [Internet]. BMJ open. BMJ Publishing Group; 2016 [cited 2019Jun3]. Available from:https://www.ncbi.nlm.nih.gov/pubmed/27188810/ ?i=2&from=/27816309/related
25. Khan TM, Khan AU, Ali I, Wu DB-C. Knowledge, attitude and awareness among healthcare professionals about influenza vaccination in Peshawar, Pakistan [Internet]. Vaccine. U.S. National Library of Medicine; 2016 [cited 2019Jun3]. Available from:https://www.ncbi.nlm.nih.gov/ pubmed/26845740

AROMATASE INHIBITOR LETROZOLE IN THE TREATMENT OF ENDOMETRIOSIS RELATED CHRONIC PELVIC PAIN

Farukh Bashir,[1] Khawar Abbas Chaudhry,[2] Asif Islam,[3] Mujtaba Hasan Siddiqui,[4] Muhammad Asim Rana,[5] Rizwan Elahi[6]

How to cite: Bashir F, Chaudhry KA, Islam A, Siddiqui MH, Rana MA, Elahi R. Aromatase inhibitor letrozole in the treatment of endometriosis related chronic pelvic pain. JAIMC. 2021; 19(1): 87-91.

Abstract

Background: To determine the role of an aromatase inhibitor letrozole in the women of reproductive age with endometriosis and related chronic pelvic pain.

Methodology : Sample size was defined by the study interval and number of patients treated with Aromatase inhibitor and data were analyzed prospectively and. Statistical analysis was carried out using SPSS version 19.0. Student's t test and chi-square test were used to detect significance. The level of significance was set at a p-value of <0.05. Enrolled patients were outpatients at an infertility center, hundred patients with endometriosis and previously treated patients both medically and surgically with unsatisfactory results. Endometriosis was diagnosed and scored by an initial diagnostic laparoscopy before treatment was started. Oral administration of letrozole 2.5mg, progestin norethisterone acetate 5mg, selbex 200mg three times a day and calcium citrate 1000mg and vitamin D (1000 IU) was given for 6 months. Pain scores were reported at each visit using a visual analogue scale from 0 to 10 (0: no pain; 10: maximum pain), After 3 months, pelvic pain and all reported side effects were recorded and assessed by visual analog scale.

Results: Pelvic pain score decreased significantly in response to treatment. Overall, no significant change in bone density was detected, neither any change in gonadotrophin levels was seen. Reduction in E1 and E2 was not significant. Mean age was 30.9 years with 80% of patients were nulliparous. Half of patients presented with dysmenorrhea. Patients previously received oral contraceptives (25%), GnRH agonists (25%) and Medroxyprogesterone acetate (50%) or underwent laparotomy with ovarian cystectomy (20%) or exploration (30%). At the end of treatment (3 months after start of treatment) mean visual analogue scale dropped from 7.65 at start of therapy to 6.1 (p-value < 0.005). Three months later (6 months after start of therapy), further significant drop of mean visual analogue scale has been reported (from 6.1 to 2).

Conclusion: The combination of letrozole (aromatase inhibitor), norethisterone acetate achieved marked reduction in pain score from 9 to 2 in 100 patients after 6 months of treatment. Letrozole has been shown to be effective in the treatment of endometriosis related pelvic pain with substantial improvement of pain and no recurrence of pain. On this basis, letrozole may be the medicine of choice for medical management of endometriosis.

Key Words: Endometriosis, letrozole, norethisterone acetate, pain score

1. Farukh Bashir
2. Khawar Abbas Chaudhry
3. Asif Islam
4. Mujtaba Hasan Siddiqui
5. Muhammad Asim Rana
6. Rizwan Elahi

1,2. Continental Medical College, Lahore
3. Evercare Hospital, Lahore
4. Akhtar Saeed Medical & Dental College, Lahore
5. Bahria Hospital, Lahore
6. Madina Munawwara, Saudi Arabia

Correspondence:
Dr. Farukh Bashir, Assistant Professor and Consultant Gynecologist, Continental Medical College, Lahore;
E-Mail: drfarrukhawan@gmail.com

Submission Date: 10-11-2020
1st Revision Date: 18-11-2020
2nd Revision Date: 02-12-2020
Acceptance Date: 13-12-2020

Five to ten percent women in reproductive age suffer endometriosis causing chronic pelvic pain and infertility.[1] Endometriosis is an estrogen dependent disease and the aim of treatment is to induce hypoes-trogenism or antagonizing estrogen action with gonadotrophine releasing hormone analog, birth control pills, danazole, norehindrone acetate or medroxy progesterone acetate.[1] Although treatment has resulted 50% reduction in severe pelvic pain, the recurrence rate for pelvic pain is as high as 75%.[2] Long term therapy with GnRH analog is not prac-tical due to its side effects related to hypo estroge-nism.[3] A significant

portion of patients not respon-ding to existing medical treatment for endometriosis related chronic pelvic pain, end up in hysterectomy and bilateral oophorectomy.[4] A molecular etiology of endometriosis has been proposed and an aromatase enzyme demonstrated locally in endometriotic implants found indicative of estrogen synthesis.[5] These implants could contribute to the progression of endometriosis even during treatment with GnRH analog which inhibit only ovarian production of estrogen.[6] Also, normal estrogen producing tissues (skin and adipose tissue) contain aromatase and continue to generate E2 during GnRH analog treatment.[7] Third generation aromatase inhibitor letrozole are potent and specifically suppresses estrogen production locally and systemically. These are well tolerated. Treatment with letrozole results in the resolution of endometriosis and related pelvic pain.[8] Disease stage and degree of its severity can be determined by laparoscopic scoring using ASRM scoring sheets.[9] The clinical significance of E biosynthesis in endometriosis is ex-amplified by the clinical observation that E is essential for the growth of endometriosis. We and other investigators have demonstrated abundant aromatase expression and local E production in endometriotic tissue.[10-16] Clearly there is a need for new treatment strategies for more effective suppression of local and systemic estrogen production. These findings prompted us to clinically target aromatase in endometriosis using its third-generation inhibitors. Among these inhibitors, anastrozole and letrozole were described in case reports and case series in which endometriosis was successfully treated in both postmenopausal and premenopausal women.[17-19] These results suggested that aromatase Inhibitor might treat endometriosis more effectively than GnRH analogues by supp-ression of local E formation in endometriotic tissue.

METHODOLOGY

Study Duration: Three and a half years

Study Design: Prospective. non-comparative

Data were analyzed prospectively and sample size was defined by the study interval and number of patients treated with aromatase Inhi-bitor. Statistical analysis was carried out using SPSS version 19.0. Student's t test and chi-square test were used to detect significance. The level of significance was set at $p < 0.05$.

Outpatients at an infertility center, hundred patients with endometriosis, previously treated both medically and surgically with unsatisfactory results were enrolled. Endometriosis was diagnosed and scored by an initial diagnostic laparoscopy before the start of treatment. Oral administration of letrozole 2.5mg, progestin norethisterone acetate 5mg, selbex 200mg three times a day, calcium citrate 1000mg and vitamin D (1000 IU) was given for 6 months. Pain scores were reported at each visit using a visual analogue scale from 0 to 10 (0: no pain; 10: maximum pain), After 3 months of therapy, pelvic pain and all reported side effects were recorded and assessed by visual analog scale.

RESULTS

Pelvic pain score decreased significantly in response to treatment. Overall no significant change in bone density was detected or any change in gonadotrphin levels were observed. Reduction in E1 and E2 were not significant. Mean age was 30.9 years and 80% of patients were nulliparous. Half of the patients presented with dysmenorrhea. Patients had previously received oral contraceptives (25%), GnRH agonists (25%) and Medroxyprogesterone acetate (30%) or underwent laparotomy with ovarian cystectomy (20%) or exploration (30%). At the end of treatment (3 months after start of treatment), mean visual analogue scale dropped from 7.65 from that at start of therapy to 6.1 (p-value < 0.005). Three months later (6 months after start of therapy), further significant drop of mean visual analogue scale has been reported (from 6.1 to 2).

The most important adverse effects thought to be associated with treatment causing hypoestrogenism are hot flushes and mood swings. It was reported that letrozole therapy was well tolerated.

DISCUSSION

Sampson's theory states that retrograde menstruation is the etiology of endometriosis. Nawathe et

al performed a meta-analysis of eight clinical studies that enrolled a total of 137 women.[20] The authors demonstrated that aromatase inhibitors decreased pain, reduced the size of extrauterine endometrial lesions and improved patient's quality of life when used in combination with gestagens, oral contraceptives, or gonadotropin-releasing hormone agonists (aGnRHs). One of the studies in this meta-analysis was a randomized controlled study. It showed that the use of aromatase inhibitors for six months in combination with aGnRH (1.0 mg anastrozole + 3.6 mg goserelin) was associated with a significant decrease in pain compared to aGnRH alone (3.6 mg goserelin) ($p<0.0001$), and significant improvement in patient-reported symptom severity (multi-dimensional patient scores [$p < 0.0001$]). No significant loss of bone mineral density (BMD) was detected at spine or femoral neck. There must also be a coexisting defect in immune system,[21] reduced macrophage scavenger activity,[22] as have locally produced pro inflammatory cytokines that may promote endometriosis growth. Aromatase has been found in endometriotic tissues and therapeutic effectiveness of aromatase inhibitor with advanced endometriosis is found to be effective in those previously reported as resistant to conventional therapy. Our findings are consistent with a prospective trial by Ferrero et al in which 82 women with pain secondary to rectovaginal endometriosis received letrozole and norethisterone acetate or norethisterone acetate alone for 6 months.[23] Pain intensity and deep dyspareunia were significantly lower in the letrozole group at three and 6-month intervals after initiating therapy. Patients reported recurrence of pain symptoms after completing treatment and at a 6-month follow-up visit. These findings were consistent with the one in our study. A large randomized, double-blinded study by Soysal et al compared administration of goserelin plus anastrozole to goserelin alone after surgery in 80 patients with severe endometriosis, demonstrating a significantly longer time to symptom recurrence in women who received goserelin plus anastrozole versus goserelin alone (>24 months vs. 17 months).[17] Amsterdam et al[24] used anastrozole and the combination OC Alesse to achieve significant pain relief in 14 of 15 patients with endometriosis refractory to multiple medical and surgical treatments, and in a prospective study[25] of 12 women with stage 4 endometriosis, patients reported signi-ficant improvement in dysmenorrhea and dyspareu-nia with a combination of letrozole and desogestrol. Letrozole significantly improved patients' pain scores during the course of treatment. In a prospective randomized clinical trial by Alborzi et al, pregnancy rates and recurrent endometriosis rates were compared between women with endometriosis undergoing therapy with an Aromatase Inhibitors (letrozole), a GnRH agonist (triptorelin), or no therapy.[26] There was no difference in pregnancy rates or endometriosis recurrence among the three groups. The majority of studies published to date have used Aromatase Inhibitors for a limited treatment course of 6 months. We also recommend a similar initial duration of therapy. A longer duration of therapy, however, should be considered in patients who have responded favorably and are motivated to continue therapy. Studies are needed to further elucidate minimum effective dosages, ideal length of therapy, role of long-term maintenance therapy, and the use of combination therapies with either OCs or GnRH

Table 1: *Patient Characteristics at Baseline*

Age in years	28-38
Gravidity/parity	P 0-3
PRIOR THERAPY	
Oral contraceptive pill	25
Leuprolide	25
Laproscopicablation/ cystectomy	04/16
Danazol/MPA	06/24
Presacral neurectomy	0

Table 2: *Adverse Events Associated with Treatment*

Adverse events	No of patients
1. Hot flashes	09
2. Mood swing	07
3. Headaches	06
4. Depression	06
5. Bone, joint pain	04

agonists. Hundred patients with severe pain showed that 6 months' treatment of letrozole with norethisteron, calcium and vitamin D rapidly reduces disease severity and associated pain. Only one patient reported to have recurrence of disease after one month of completion of treatment. There was no change in estrogen and gonadotrophin levels and no significant bone loss was detected during and after treatment.

No patient withdrew from the study. Norethisterone acetate may have contributed to pain relief in this study. That agent alone has been shown to relieve pelvic pain but not in advanced and refractory cases. The ovarian effects of prolonged exposure to letrozole alone are not known. In our study, monthly pelvic scan during and after 6 months regimen of letrozole plus norethisteron acetate did not reveal any evidence of ovarian cyst formation. The results obtained were promising and constitute the rationale for further investigation of this regimen. Randomized controlled trials are needed to establish the role of letrozole in endometriosis. Future studies are necessary to determine pregnancy rates after long-term Aromatase inhibitor treatment for endometriosis. Our study and previously published studies suggest that endometriosis responds favorably to treatment with Aromatase Inhibitors. Aromatase inhibitors are well tolerated by patients and may represent a promising new therapy for endometriosis. Further evaluation and development are needed to evaluate the role of Aromatase Inhibitors in the management of endometriosis-related pelvic pain. Although adhesion-related pain may have contributed to chronic pain, all patients in this study had undergone at least one laparoscopic procedure for diagnostic or therapeutic purposes and the majority of patients who received prolonged therapy with letrozole had also undergone at least one laparotomy before treatment. The study participants were relatively homogeneous in their prior surgical history and thus we did not evaluate the correlation between prior surgical interventions with response to Aromatase Inhibitors.

CONCLUSION

The combination of letrozole and norethisterone acetate achieved marked reduction in pain relief who have not responded previously to currently available treatment. On this basis, letrozole may be recommended as a potential drug for medical management of endometriosis.

REFERENCES

1. Littman BA, Smotrich DB, Stillman RJ. Endometriosis. In: Becker KL,ed. Principles and practice of endocrinology and metabolism, 2d ed.Philadelphia: J.B. Lippincott Company, 1995:906–9.
2. Surrey ES, Hornstein MD. Prolonged GnRH agonist and add-back therapy for symptomatic endometriosis: long-term follow-up. Obstet Gynecol 2002; 99:709-9.
3. Pierce SJ,Gazwani MR,Farquharson RG.Long term use of gonadotrophin-releasing hormone analogue and hormone replacement therapy in the management of endometriosis:a randomized,placebo controlled,double blind trial.Ferti Steril 2000;74: 534-9.
4. Sidell N, Han SW, Parthasarathy S. Regulation and modulation of abnormal immune responses in endometriosis. Ann NY Acad Sci 2002;955:159–73.
5. Zeitoun KM, Bulun SE, Aromatase: a key molecule in the pathophysiology of endometriosis and a therapeutic target.Fertil Steril1999;72:961-9
6. Bulun SE, Zeitoun K, Takayama K, Noble L, Michael D, Simpson E,et al. Estrogen production in endometriosis and use of aromatase inhibitors to treat endometriosis. Endo Rel Cancer 1999;6: 293–301.
7. Meinhardt U,Mullis PE.The essential role of the aromatase/p450 arom.Semin Reprod Med 2002;20; 277-84.
8. Goss PE,Strasser K.Aromatase inhibitor in the treatment and prevention of breast cancer.J Clin Oncol.. 2001;19:881-94
9. American society of Reproductiv Medicine.Revised American Society for Reproductiv Medicine classification of endometriosis .1996. Fertil Sertil 1997; 67;817-21
10. Zeitoun K, Takayama K, Michael MD, Bulun SE. Stimulation of aromatase 450 promoter (II) activity in endometriosis and its inhibition in endometrium are regulated by competitive binding of steroidogenic factor-1 and chicken ovalbumin upstream promoter transcription factor to the same cis-acting

element. Mol Endocrinol. 1999;13:239–253. [PubMed].

12. Yang S, Fang Z, Suzuki T, Sasano H, Zhou J, Gurates B, et al. Regulation of aromatase P450 expression in endometriotic and endometrial stromal cells by CCAAT/ enhancer binding proteins (C/EBPs): decreased C/EBPbeta in endometriosis is associated with overexpression of aromatase. J Clin Endocrinol Metab. 2002;87:2336–2345. [PubMed]
13. Gurates B, Sebastian S, Yang S, Zhou J, Tamura M, Fang Z, et al. WT1 and DAX-1 inhibit aromatase P450 expression in human endometrial and endometriotic stromal cells. J Clin Endocrinol Metab. 2002; 87:4369–4377. [PubMed]
14. Fang Z, Yang S, Gurates B, Tamura M, Simpson E, Evans D, et al. Genetic or enzymatic disruption of aromatase inhibits the growth of ectopic uterine tissue. J Clin Endocrinol Metab. 2002; 87: 3460–3466. [PubMed]
15. Bulun SE, Yang S, Fang Z, Gurates B, Tamura M, Zhou J, et al. Role of aromatase in endometrial disease. J Steroid Biochem Mol Biol. 2001; 79: 19–25. [PubMed]
16. Kitawaki J, Noguchi T, Amatsu T, Maeda K, Tsukamoto K, Yamamoto T, et al. Expression of aromatase cytochrome P450 protein and messenger ribonucleic acid in human endometriotic and adenomyotic tissues but not in normal endometrium. Biol Reprod. 1997;57:514–519. [PubMed]
17. Bulun SE, Imir G, Utsunomiya H, Thung S, Gurates B, Tamura M, et al. Aromatase in endometriosis and uterine leiomyomata. J Steroid Biochem Mol Biol. 2005;95:57–62. [PubMed]
18. Takayama K, Zeitoun K, Gunby RT, Sasano H, Carr BR, Bulun SE. Treatment of severe postmenopausal endometriosis with an aromatase inhibitor. Fertil Steril. 1998;70:1183–1184. [PubMed]
19. Soysal S, Soysal ME, Ozer S, Gul N, Gezgin T. The effects of post-surgical goserelin alone in patients with severe endometriosis: a prospective randomized trial. Hum Reprod. 2004;19:160–167. [PubMed]
20. Lall SS, Kamilva G, Mukherji J, De A, Ghosh D, Majhi AK. Aromatase inhibitors in recurrent ovarian endometriomas: a report of five cases with literature review. Fertil Steril. 2011;95:291. [PubMed]
21. Nawathe A, Patwardhan S, Yates D, et al. Systematic review of the effects of aromatase inhibitors on pain associated with endometriosis. BJOG. 2008; 115: 818– 822. [PubMed]
22. Barcz E,Kaminski P,Marianowski L.Role of cytokines in pathogenenisis of endometriosis,Med Sci Monit 2000;6:1042-6
23. Sidell N,Han SW,Paethasarathy12. Gurates B, Sebastian S, Yang S, Zhou J, Tamura M, Fang Z, et al. WT1 and DAX-1 inhibit aromatase P450 expression in human endometrial and endometriotic stromal cells. J Clin Endocrinol Metab. 2002;87: 4369–4377. [PubMed]
24. Ferrero S, Camerini G, Seracchioli R, Ragni N, Venturini PL, Remorgida V. Letrozole combined with norethisterone acetate compared with norethisterone acetate alone in the treatment of pain symptoms caused by endometriosis. Hum Reprod. 2009; 24: 3033–3041. [PubMed]
25. Amsterdam LL, Gentry W, Jobanputra S, Wolf M, Rubin SD, Bulun SE. Anastrozole and oral contraceptives: a novel treatment for endometriosis. Fertil Steril. 2005;84:300–304. [PubMed]
26. Remorgida V, Abbamonte LH, Ragni N, Fulcheri El, Ferrero S. Letrozole and desogestrol-only contraceptive pill for the treatment of stage IV endometriosis. Aust N Z J Obstet Gynaecol. 2007;47:222 – 225. [PubMed]
27. Alborzi S, Hamedi B, Omidvar A, Dehbashi S, Alborzi S, Alborzi M. A comparison of the effect of short-term aromatase inhibitor (letrozole) and GnRH agonist (triptorelin) versus case control on pregnancy rate and symptom and sign recurrence after laparoscopic treatment of endometriosis. Arch Gynecol Obstet. 2011; 284:105–110.

EFFECT OF DERANGED LIVER ENZYMES ON THE CLINICAL COURSE AND OUTCOME OF COVID-19 AT JINNAH HOSPITAL, LAHORE, PAKISTAN

Rabia Arshad,[1] Saadat Ullah,[2] Muhammad Aleem,[3] Junaid Babar,[4] Sanaa Khurshid,[5] Tanvir us Salam[6]

How to cite: Arshad R, Ullah S, Aleem M, Babar J, Khurshid S, Salam T. Effects of deranged liver enzymes on the clinical course and outcome of COVID-19 at Jinnah Hospital, Lahore, Pakistan. JAIMC. 2021; 19(1): 92-96.

Abstract

Background: The COVID-19 first case was documented in Pakistan in February 2020. Among other extra-pulmonary manifestations, deranged liver enzymes are frequently observed.

Objective: To determine the association of deranged liver enzymes with the severity and prognosis of COVID-19 disease.

Methodology: This descriptive cross-sectional research was conducted at the Corona Unit of Jinnah hospital, Lahore. 60 patients (Male 33, Female 27) diagnosed as COVID- 19 on RT-PCR, were selected and included in the study and all patients were advised LFTs at the time of the first presentation and descriptive statistics were applied to find its association with COVID-19.

Results: 60 COVID-19 patients (Male 33, Female 27) with mean age of 52.16 ± 15.02 years, were included in the study. On the basis of severity classification, 15 % (N = 9) patients were mild (mean age 46.59 ± 15.04 years), 26.6 % (N = 16) were moderate (mean age 47.12 ± 16.01 years), 40 % (N = 24) patients were severe (mean age 54.54 ± 14.11 years), and 18.33 % (N = 11) patients were critical (mean age 56.22 ± 17.07 years). Logistic Regression analysis showed increase in ALT (p = 0.002) and AST (p = 0.001) were associated with raised d-Dimer (p=0.003) levels, increase in age (p = 0.004), more intensive care unit admissions and high mortality.

Conclusion: Deranged liver enzyme(ALT and AST) and d-Dimer levels along with increased age, and co-morbidities were found to be highly correlated with COVID-19 severity.

Keywords: LFTs; AST; ALT; COVID-19.

COVID-19 disease began as an outbreak in late 2019 in China and started spreading to other parts of the world as a pandemic in early 2020.[1] It began as an outbreak in Pakistan in February 2020 and was declared as a global threat by WHO in March 2020.[2,3] According to world-meter of corona-virus, by mid-August 2020, this virus caused 289,215 cases and 6,175 deaths in Pakistan.[2] There is a significant mortality rate, disease burden, and adverse economic and health sector outcome of this virus.[4,5]

There are several pulmonary and extra-pulmonary manifestations of this virus.[6] Deranged liver function tests can be one of the prominent extra-pulmonary manifestations of this disease.[9] The de-rangement of LFTs is found to be due to the binding of SARS-CoV-2 to ACE-2 receptors present at the ductal system of the liver which causes microvascular steatosis, micro-thrombosis, lobular necrosis, and blockage of lobular and portal activity.[7,8,10,11]

The clinical presentation noted in patients having COVID-19 with deranged liver function enzyme is severe pneumonia. Medications that set of

1. Rabia Arshad
2. Saadat Ullah
3. Muhammad Aleem
4. Junaid Babar
5. Sanaa Khurshid
6. Tanvir us Salam

1,2. Medical Officer, Medical Unit I JHL
3. Endocrinology Fellow, JHL
4,6. Medical Unit I, Jinnah Hospital Lahore
5. Post Graduate Trainee, Nephrology Unit, JHL

Correspondence:
Dr. Rabia Arshad, *Medical Officer, Medical Unit I JHL*

Submission Date: 20-11-2020
1st Revision Date: 12-12-2020
Acceptance Date: 18-12-2020

damage to liver including NSAIDS, RIBAVARIN, antibiotics also augment the severity of the disease.[12] Unmanageable immune manifestation and cytokine storm mediated inflammation results in injury to the liver causing derangement of liver biochemical markers.

Individuals with COVID-19 have increased levels of, IL2, IL6, IL7, IL10, TNF- alpha TH17, CD8 T cells, infection inducible protein[10], CRP, granulocyte colony-stimulating factors that lead to liver injury.[11,13]

Due to the increasingly COVID-19 burden on the health care system demanding patient-focused quality of care based on disease severity is of the highest importance. Hence pathological factors predictive of the severity of disease would be a keystone in grading resources.

Review of the literature showed that deranged LFTs were found to be in at least 15-45% of COID-19 patients admitted in ICU or HDU.[11,14,15] Therefore following this rationale, the present study was conducted to determine the derangement in liver function tests (LFTs) in COVID-19 patients admitted at the Corona Unit of Jinnah hospital, Lahore, and its association with severity and prognosis of the disease.

METHODOLOGY

This descriptive cross-sectional study was conducted after taking informed consent and ethical approval at the Corona Unit, Jinnah Hospital/AIMC, Lahore, over 45 days(from 20th June 2020 to 3rd August 2020).The sample size was not calculated due to the limited data available. A sample of 100 COVID-19 patients were included using a non-probability consecutive sampling technique. Inclusion Criteria for the study includes

- COVID-19 confirmed patients as per WHO interim guidance & meeting the following criteria: Epidemiological history, (b) Fever or other pulmonary symptoms, (c) Typical chest X-ray appearance, and (d) RT-PCR + for SARS-CoV-2.3
- Willing to participate in the study.

Excluding those with

- Pre-existing liver diseases.
- Liver function tests not performed on the first presentation.

A total of 60 COVID-19 confirmed patients were included in this study as per selection criteria. All patients were advised LFTs at the time of the first presentation, including, serum Alanine Aminotransferases (ALT), Aspartate Aminotransferases (AST), total bilirubin, ferritin, creatinine, LDH, and D-dimer. Patients were divided into mild, moderate, severe, and critical categories based on severity as issued by NHSRC, the government of Pakistan. The mild and moderate COVID-19 patients were taken as non-severe patients while severe and critical patients were considered as severe patients.

Data were collected using pre-tested pre-designed proforma and the following details were collected and recorded: demographic data, age, gender, contact history, symptoms, medical history, length of hospital stay, mortality, qSOFA values, chest radiograph findings, and LFTs.

Quantitative datawere presented by mean ± SD & will be compared using the t-test and Mann Whitney U-test. Qualitative data were presented by frequency and percentages& will be compared using Chi-square or Fisher exact test. Logistic Regression was applied on significant association of continuous variables with severity.

RESULT

60 COVID-19 patients (Male 33, Female 27) with a mean age of 52.16 ± 15.02 years, were included in the study.On the basis of severity, 15 % (N = 9) patients were mild (mean age 46.59 ± 15.04 years), 26.6 % (N = 16) were moderate (mean age 47.12 ± 16.01 years), 40 % (N = 24) patients were severe (mean age 54.54 ± 14.11 years), and 18.33 % (N = 11) patients were critical (mean age 56.22 ± 17.07 years). The age (p = 0.004), and co-morbidities (p = 0.001)differences were significant between severe and non-severe patientsbut insignificant gender (p =

0.541), contact history (p = 0.433), symptomand length of hospital stay (p=0.345)differences were found between severe and non-severe patients.The most common symptoms were fever, cough and fatigue. The mortality rate was 2%. TheALT (p = 0.002), AST (p = 0.001), and D-dimer (p=0.003) for severe patients were significantly higher while length of hospital stays, serum creatinine, LDH, ferritin, bilirubin and qSOFA values were statistically insignificant as compared to the non-severe patients. The predominant feature on chest radiograph for severe patients was diffuse lung infiltration while the predominant feature for non-severe patients was normal appearance to peripheral lung involvement.

Logistic Regression analysis showed that increase in age(p = 0.004), co-morbidities (p=0.003) and increase in ALT (p = 0.002), AST (p = 0.001), and D-dimer (p=0.003) levels were significantly associated with increased severity of disease.

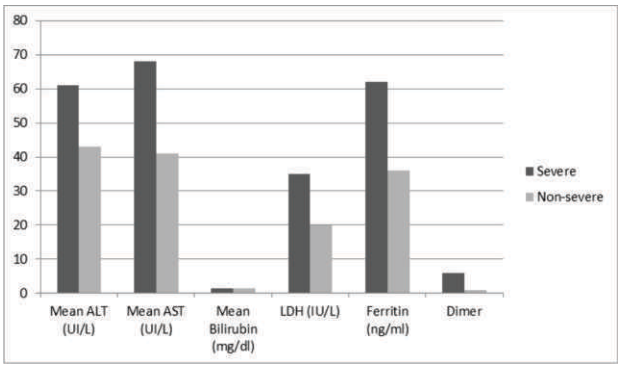


Figure 1: *Comparison of LFTs Levels*

DISCUSSION

The local data is limited regarding derangement in liver function tests in COVID-19 patients admitted at HDU or ICU of Pakistani hospitals. Therefore, the aim was to determine the derangement in LFTs in COVID-19 subjects admitted at the Corona Unit of Jinnah hospital, Lahore, and its association with the severity and prognosis of the disease.

The results showed that COVID-19 was more

Table 1: *Comparison of different Parameters*

Variable	Severe % (N)	Non-Severe % (N)	Total % (N)	P
Age	55.14 ± 16.01	47.43 ± 16.01	52.16 ± 15.02	0.004
Gender (Male/Female)	19/16	14/11	33/27	0.541
Positive Contact History	17	18	35 (35)	0.433
BMI (kg/m^2)	26	24	25± 2	0.344
Smoking	3	2	5 (5%)	0.965
Co-morbidities				
No Co-morbidities	6	3	9	
Diabetes Mellitus	15	10	25	
Hypertension	14	6	20	0.003
Ischemic Heart Disease	6	3	9	
Others	7	4	11	
Length of Hospital Stay	32.3 ± 12.1 days	29.1 ± 12.6 days	29.3 ± 11.4 days	0.433
ALT (IU/L)	61.22 (± 34.13)	43.76 (± 25.67)	48.12 (±27.12)	0.002
AST (IU/L)	68.11 (± 25.12)	41.33 (± 17.60)	45.12 (±19.32)	0.001
Bilirubin (mg/dl)	1.4678 (± 0.91)	1.4111 (±0.31)	1.3566 (±0.34)	0.567
LDH (IU/L)	356.13 (± 257.34)	201.88 (± 121.11)	245.73 (± 287.13)	0.345
Ferritin (ng/ml)	422.231 (± 532.23)	367.599 (±634.11)	3.15.356 (±4.11)	0.542
D-dimer (mg/L)	2.34 (± 2.76)	0.54 (±2.54)	1.44 (±2.11)	0.001
Creatinine (mmol/L)	65.21 (± 2.76)	65.11 (± 2.87)	65.56 (± 2.61)	0.766
qSOFA Score	0.1 ± 0.21	0.0 ± 0.10	0.2 ± 0.20	0.345
Mortality	2	0	2	0.008
Predominant Chest X-ray				
Peripheral involvement	13	14	27	
Peripheral & Basal	8	5	13	0.855
Diffuse infiltration	19	1	20	

common in males as compared to females; this is in agreement with the findings of a recently conducted study in China and Pakistan, where it was also found that COVID-19 was more common in male as compared to female.[16,17] The mean age was 53.61 ± 16.04 years, this is also in agreement with the findings of a recently conducted study in China and Pakistan,[16-19] where it was also found that COVID-19 patients' mean age was around 50 years, however, this is in contrast with the findings of the recently conducted study in France, where it was also found that COVID-19 patients' mean age was around 45 years.[20]

Patients were divided into mild, moderate, severe, and critical categories based on severity as issued by NHSRC, the government of Pakistan. The results showed that 41 % of patients were non-severe, while 58% were severe patients. This is in contrast with the findings of recently conducted two studies in China, where the majority of the patients were non-severe.[17,21]

The age and co-morbidities differences were significant between severe and non-severe patients, but insignificant gender, symptoms, length of hospital stay, and contact history differences were found between the two groups. The most common symptoms were fever, cough, and fatigue. The mortality rate was 2%. This is in agreement with the findings of a recently conducted study in China and Pakistan,[16-19] where it was found that increasing age and co-morbidities are linked with the severity of disease but not the gender or contact history.

The ALT, AST, and D-dimer for severe patients were significantly higher while serum creatinine, LDH, ferritin, bilirubin, and qSOFA values were statistically insignificant as compared to the non-severepatients. The predominant feature on chest radiograph for severe patients was diffuse lung infiltration while the predominant feature for non-severe patients was a normal appearance to peripheral lung involvement. This is in agreement with the findings of recently conducted two studies in China.[17,21] However, this is in contrast with the findings of another recently conducted study in China,[23] where it was also found that ALT, AST, and bilirubin levels were not significantly associated with the severity of COVID-19 disease. The results of the present study showed that LFTs can be used to define the severity of COVID-19 admitted patients and the potential need for intensive care.

Limitations of Study

1. Limited local studies were available and sample size is small which might not be projecting the whole disease burden of our population.
2. Follow up of liver enzymes were not included in study which demand a separate follow up sudy on the course of liver function derangement during hospital stay .
3. This study has high number of severe and critical patients because those with mild and moderate disease with no comorbidities were advised home isolation and observation.

However, within these limitations, the result of the present study showed that deranged liver enzyme levels were found to be highly correlated with COVID-19 disease severity and prognosis

CONCLUSION

An increase in age and comorbidity presence is significantly associated with developing severe COVID-19 disease. Patients with deranged liver enzymes (ALT and AST) are at higher risk to develop severe disease, offering it a potential marker for anticipating the severity of the disease. The correlation between COVID 19 severity and liver injury also demands its routine monitoring in COVID 19.

Acknowledgement

Dr Tanveer us Salam, Head Medical Unit 1

Dr Abbas Raza, Head Medical Unit 2

Conflict of Interest: None

Funding Statement: None

REFERENCES

1. Rothan HA, Byrareddy SN: The epidemiology and

pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of autoimmunity. 2020:102433.

2. Waris A, Khan AU, Ali M, Ali A, Baset A: COVID-19 outbreak: current scenario of Pakistan. New Microbes and New Infections. 2020:100681.
3. Organization WH: Mental health and psychosocial considerations during the COVID-19 outbreak, 18 March 2020. World Health Organization; 2020.
4. Ji Y, Ma Z, Peppelenbosch MP, Pan Q: Potential association between COVID-19 mortality and health-care resource availability. The Lancet Global Health. 2020, 8:e480.
5. Miller IF, Becker AD, Grenfell BT, Metcalf CJE: Disease and healthcare burden of COVID-19 in the United States. Nature Medicine. 2020, 26:1212-1217.
6. Cheng H, Wang Y, Wang GQ: Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. Journal of medical virology. 2020.
7. Bangash MN, Patel J, Parekh D: COVID-19 and the liver: little cause for concern. The Lancet Gastroenterology & Hepatology. 2020, 5:529.
8. Diaz JH: Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. Journal of Travel Medicine. 2020.
9. Tolouian R, Vahed SZ, Ghiyasvand S, Tolouian A, Ardalan M: COVID-19 interactions with angiotensin-converting enzyme 2 (ACE2) and the kinin system; looking at a potential treatment. Journal of Renal Injury Prevention. 2020, 9:e19-e19.
10. Zhang Y, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q: Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single centre in Wuhan city, China. Liver International. 2020.
11. Li J, Fan J-G: Characteristics and mechanism of liver injury in 2019 coronavirus disease. Journal of Clinical and Translational Hepatology. 2020, 8:13.
12. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, Li Z, Zhou G, Gou J, Qu J: COVID-19: abnormal liver function tests. Journal of hepatology. 2020.
13. Omrani-Nava V, Maleki I, Ahmadi A, Moosazadeh M, Hedayatizadeh-Omran A, Roozbeh F, Nahanghi H, Alizadeh-Navaei R: Evaluation of Hepatic Enzymes Changes and Association with Prognosis in COVID-19 Patients. Hepatitis Monthly. 2020, 20.
14. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, Zhang Y, Huang S, Liu Z, Cheng J: Clinical features of COVID-19-related liver damage. Clinical Gastroenterology and Hepatology. 2020.
15. Zhang C, Shi L, Wang F-S: Liver injury in COVID-19: management and challenges. The lancet Gastroenterology & hepatology. 2020, 5:428-430.
16. Ahmed M, Umar M, Sufyan A, Zeb S, Ahmad H, Shahid R: Liver Function Tests; a Marker of Severity in Covid 19 Patients. Austin Hepatol. 2020, 5:1013.
17. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020, 395:497-506.
18. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, Fan Y, Zheng C: Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. The Lancet Infectious Diseases. 2020.
19. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L: Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology. 2020: 200642.
20. Gautret P, Lagier J-C, Parola P, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Dupont HT: Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International journal of antimicrobial agents. 2020:105949.
21. Guan W-j, Liang W-h, Zhao Y, Liang H-r, Chen Z-s, Li Y-m, Liu X-q, Chen R-c, Tang C-l, Wang T: Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. European Respiratory Journal. 2020, 55.
22. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, Liu L, Shan H, Lei C-l, Hui DS: Clinical characteristics of 2019 novel coronavirus infection in China. MedRxiv. 2020.
23. Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T: Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine. 2020.

SEGREGATION OF CERVICAL PATHOLOGY WITH UTILITY OF PAP SMEAR EXAMINATION

Nosheen Khurram,[1] Asma Adnan,[2] Sofia Khan,[3] Noshin Wasim Yusuf[4]

How to cite: Khurram N, Adnan A, Khan S, Yusuf NW. Segregation of cervical pathology with utility of PAP smear examination. JAIMC. 2021; 19(1): 97-102.

Abstract

Background: Cervical cancer is one of the leading cause of death of women in developing countries. A key factor linked to the relatively high incidence of cervical cancer in these population is the lack of awareness and access to preventive methods. It is well known that cervical cancer mortality and morbidity could be significantly reduced with an active pap smear screening program.

Present study was conducted to determine the importance of pap smear for segregation of non-epithelial, premalignant and malignant lesions of the cervix for purpose of appropriate treatment and reduction of mortality and morbidity related to it.

Methodology: This is a validation study of four hundred and twenty five cases of pap smear conducted in the Department of Pathology, Rashid Latif Medical College, in collaboration with Gynecology departments of Arif Memorial Hospital and Hameed Latif Hospital over period of one year (from January 2019 to December 2019). Pap stain was done on all cervical smears and reported as per 2014 Bathesda system.

Results: A total of 425 cases of Pap smears were received. The frequency of epithelial abnormalities was 3.76%. The age group of 41-50 years showed the highest epithelial abnormalities. Out of the 425 cases, 22(5.17%) showed changes of atrophy and196(46.11%)cases showed inflammatory/reactive changes.

Conclusion: Pap smear turn out to be an economical, safe and practical diagnostic tool for cervical pathology diagnosis and early detection of cervical cancer.

Keywords: Bethesda system, Cervical cancer, Epithelial abnormality, Pap smear

Cervical pathology is very common globally and especially in developing countries and one of the leading cause of cancer related deaths[1]. According to data obtained from world-wide analysis revealed that approximately 570,000 cases of cervical cancer and 311,000 deaths from disease occurred in 2018.[2]

With changes in the life style and demographic profile in developing countries, inflammatory conditions of the genital tract especially cervix are emerging as an important health problem which demand appropriate treatment program.[3] The main purpose of cervical cancer screening is early detection of preinvasive lesions which will ultimately lead to decrease in incidence and mortality from invasive cervical cancer. This concept is quite useful for the last many years.[4]

There are many risk factors associated with development of dysplastic cells in cervix. Among those Human Papilloma virus is the primary factor. Other factors include first intercourse at an early age, multiple sexual partners, smoking and compromised immune system.[5]

The papanicoloau test is economical, easy to use and economical technique in which cells are taken from cervix. This method is widely used for detection of cervical pathology. A regular pap smear taken and interpreted by a qualified health care provider is the only way to diagnose any cervical pathology related to inflammation or dysplastic changes which can be dealt with appropriately.

1. Nosheen Khurram 2. Asma Adnan
3. Sofia Khan 4. Noshin Wasim Yusuf
1-4. Department of Pathology, Rashid Latif Medical College Lahore

Correspondence:
Dr. Nosheen Khurram, *Department of Histopathology, Rashid Latif Medical College, Lahore, E-Mail: nosheenkhurram@gmail.com*

Submission Date: 12-09-2020
1st Revision Date: 15-10-2020
Acceptance Date: 29-11-2020

METHODOLOGY

Four hundred and twenty-five cases of pap smear were received from department of obstetrics and gynecology of Arif Memorial Hospital, and Hameed Latif Hospital, Lahore. All these pap smears were adequate for cytological evaluation. Unsatisfactory pap smears due to low cellula-rity and presence of obscuring blood and mucinous material were excluded. Already diagnosed patients of cervical malignancy were also not included in study. Smears were taken by trained doctors using modified Ayres wooden spatula which was inserted and rotated 3600 over cervix. Both ectocervix and endocervix were sampled. Slides were prepared, labeled, fixed in 95% ethyl alcohol immediately and subsequently stained by Pap stain.[6] After staining, slides were mounted with DPX (distrene dibutyl phthalate xylene). Smears were screened for adequacy criteria. Conventional smears should contain 8000 to 12000 well preserved and well visualized squamous epithelial cells. Finally diagnosis was made by two cytopathologists according to the 2014 Bethesda system.[7]

RESULTS

The present study was carried out on 425 women in the Department of Pathology, Rashid Latif Medical college during a period from January 2019-December 2019. The smears were reported according to the guidelines given by The Bethesda System (2014)Table 1.

The age range in the present study ranges from 19 to 77 years with a mean age of 38 years. Majority of women were in the 31-40 years age group comprising of 149 cases (35%). The youngest female was 19 years of age and the oldest was 77 years of age Figure 1.

Out of 425 patients, 96 (22.5%) were asymptomatic while 329 (77.4%) presented with various symptoms. Amongst the symptomatic cases, discharge p/v, abdominal pain and irregular menstruation were the most common presenting complaints, comprising 20.2%, 15.5%, and 14.5%, respectively. Other complaints were Menorrhagia (11.7%), something coming out of vaginum (7.2%),Amenorrhea (6.3%), burning micturition (1.1%)andpost- menopausal bleeding (0.47%) Figure 2.

There were 409 cases (96.23%) which showed no significant epithelial abnormalities. Epithelial abnormalities like ASCUS, LSIL, HSIL, Adenocarcinoma- not otherwise specified and Squamous cell carcinoma were found in 16 cases (3.76%).

Current study revealed ASCUS was the most common abnormality (1.64%) Figure 3, followed by HSIL (0.94%)Figure 4 and squamous cell carcinoma (0.70%) Figure 5. The frequency of LSIL was 0.23% and of Adenocarcinoma NOS was 0.23%.

Out of 425 cases, 158 cases had normal smear. NILM with reactive cellular changes associated with inflammation were noted in 196 cases (46.11%) Figure 6. There were 22 cases (5.17%) showed changes of atrophy. There were 19 cases (4.4%) of bacterial vaginosis, 4 cases (0.94%) of candida and 7 cases (1.6%) showing mixed infection. Infection by trichomonas vaginalis was seen in 1 case (0.23%). Changes of viral infection were seen in 2 cases (0.4 %). Majority of inflammatory smears were found in 31- 40 yeras age group (18.5%), followed by 21-30 years age group (12%).

Out of 15 cases that showed epithelial abnormality, 12 came to histology for diagnosis. Out of 4 cases of ASCUS, one was reported as SCC, one was reported CINII and 2 were reported as CIN I. There were 4 cases of HSIL on cytology, out of which 2 were reported as CIN I, one was reported as CIN II, one was reported as Squamous cell carcinoma on histology. All cases of squamous cell carcinoma were confirmed on biopsy as cervical malignancy. One case of adenocarcinoma diagnosed on cytology revealed adenocarcinoma involving cervix as well as uterus on histological examination.

Table 1: Cytological Interpretation as per the 2014 Bethesda System for Reporting Cervical Cytology

Interpretation as:	No. of patients	Percentage (%)
Negative for intraepithelial lesion or malignancy		
Normal smears	**158**	**37.18%**
Non neoplastic findings:		
• Atrophy	**22**	**5.18%**
• Reactive cellular changes associated withInflammation (Includes typical repair)	**196**	**46.12%**
Organisms:		
• Trichomonas vaginalis	**1**	**0.23%**
• Fungal organisms morphologically consistent with Candida spp.	**4**	**0.94%**
• Shift in flora suggestive of bacterial vaginosis	**19**	**4.47%**
• Mixed infection	**7**	**1.65%**
• Cellular changes associated with virus	**2**	**0.47%**
Epithelial cell abnormalities		
Squamous cell:		
• Atypical squamous cells – of undetermined significance (ASC-US)	**7**	**1.65%**
• Low-grade squamous intraepithelial lesion (LSIL)	**1**	**0.23%**
• High-grade squamous intraepithelial lesion (HSIL)	**4**	**0.94%**
• Squamous cell carcinoma	**3**	**0.71%**
Glandular cell:		
• Adenocarcinoma Not otherwise specified (NOS)	**1**	**0.23%**
Total	**425**	**100%**

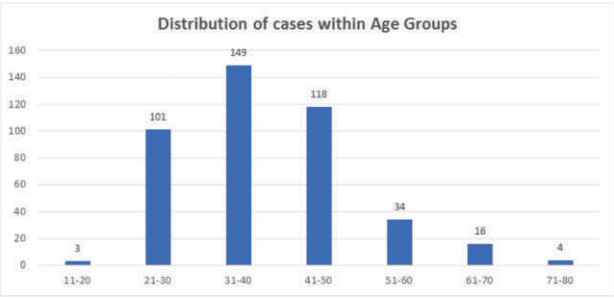


Figure 1: *Distribution of Cases within Various Age Groups*

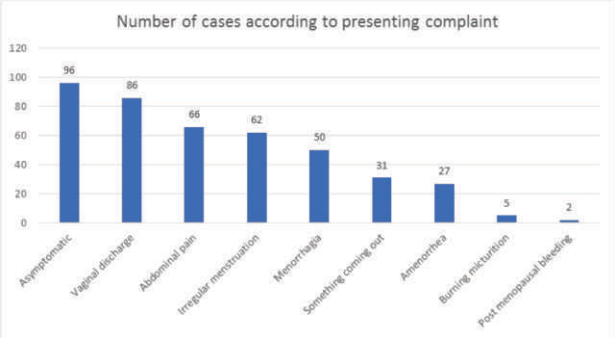


Figure 2: *Distribution of Cases According to Various Presenting Complaints*

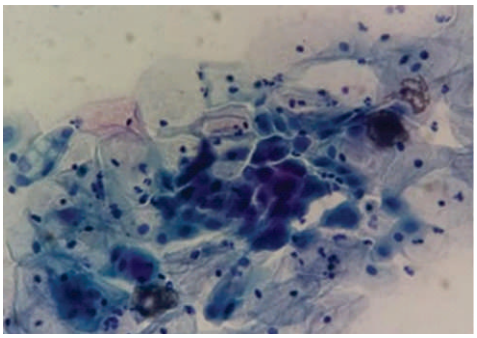


Figure 3: *Showing ASCUS Against Background of Inflammatory Cells on Pap Smear. (Pap Stain,40X)*

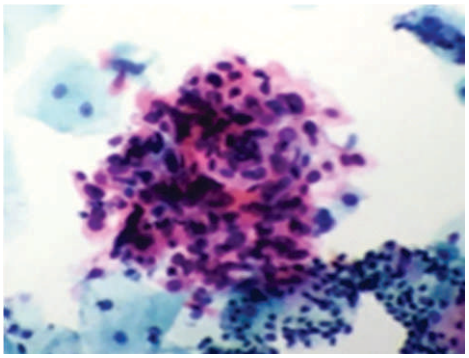


Figure 4: *Pap Smear Showing HSIL Along with Inflammatory Cells (Pap Stain,40X)*

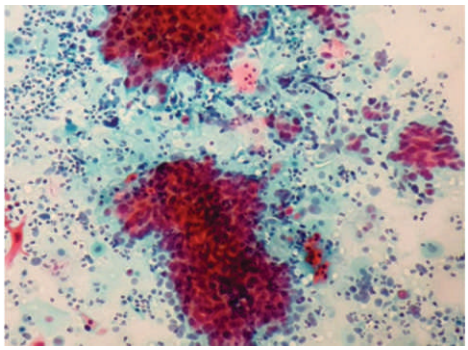


Figure 5: *Showing Squamous Cell Carcinoma in Cervical Smears (Pap Stain,20X)*

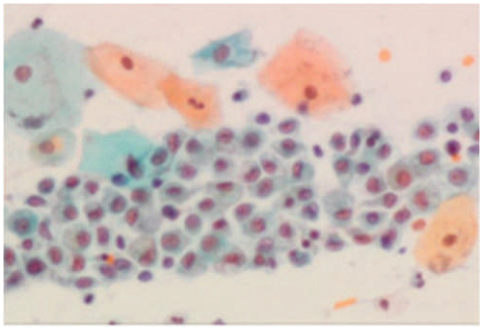


Figure 6: *Pap Smear Showing NILM (Pap Stain,40X)*

DISCUSSION

There are numerous screening test for diagnosis of cervical pathology like Pap smear, liquid Pap cytology, visual inspection of cervix after Lugol's Iodine, automated cervical screening techniques,and acetic acid application, speculoscopy, and cervicography. In spite of variousmethods, exfoliative cytology has been regarded as the gold standard for cervical screening programs.[3]

In cervical smear examination adequacy criteria should be fulfilled. Inadequate smears contain low squamous cellularity obscured by polymorphs and RBCs. Atrophy of tissue and retraction of squamocolumnar junction is caused by deficiency of estrogen which lead to greater incidence of unsatisfactory smears. In present study only smear satisfactory for evaluation were included.[8]

In present study, majority of cases were in the 31-40 years age group (35.05%) and were found to be similar with the study of Gandhi etal (38.5%),[5] Bhojani et al (34.75%),[9] Sachan et al(30.66%),[10] Chakraborty et al(33.4%),[11] Nandini et al(32%),[12] and Saha et al (27.1%).[13] Other common affected age group was 41-50 years age group (27.76%) which was comparable with the study of Gandhi et al (24.1%),[5] Bhojani et al (20.5%),[9] Sachan et al (20.3%),[10] Chakrabotry et al (28%),[11] Nandini et al (30%),[12] and Saha et al (23.3%).[13]

In present study most common presenting complaint was discharge per vaginum followed by abdominal pain, irregular menstruation, menorrhagia, burning micturition and post-menopausal bleeding. This pattern is comparable to other studies (Bhojani et al,[9] Sachan et al,[10] Chakraborty et al,[11] and Bisht et al).[14]

There were 16 cases with epithelial abnormalities in the present study (3.76%). The frequency of various epithelial abnormalities were, 5% in Balet al15,4% in Khattak et al,[16] 3.65 % inGandhi et al,[5] 3.2% in Gupta et al,[17] 3.08% in Kalyani et al,[18] and Das et al (2.43%).[19] All findings are quite comparable with present study. The frequency of epithelial abnormalities in our part of the world including Pakistan and India varies from 1.2 to 5.9%, as stated in a study by Mulay et al.[20]

ASCUS was the most commonly seen epithelial abnormality in present study (1.64%), which was found similar to the study done by Gandhi et al (1.36%),[5] Bajpai et al (2%)[21] and Kalyani et al (1.5%)[b]. HSIL was the second common abnormality noted with 0.94% in the present study. Results of HSIL cases revealed by Gupta et al(0.91%),[17] Sachan et al(0.48%),[10] Gandhiet al(0.78%),[5] Bajpai et al (0.6%),[21] Mulay et al (0.6%),[20] and Nandini et al (2.7%)[12] are quite similar.The presence of HSIL is more likely to progress to invasive cancer, whereas generally low-grade lesions regress spontaneously, creates a warning that eradicating HSIL is critical for cancer prevention. Therefore, we should put more efforts in detecting HSIL at an early stage before it grows to invasive cancer. The frequency of invasive cancers was 0.94% in the present study, while Gandhi et al revealed (0.26%)[5], Gupta et al (0.28%),[17] Bajpai et al (0.3%),[21] Bhojani et al(0.75%),[9] and Saha et al(1.04%).[13]

In the present study, the frequency of cervical dysplasia (LSIL & HSIL) and cervical cancer in women with presenting complaints of lower abdominal pain, discharge per vaginum, something coming out p/v and menorrhagia was 3%, 1.1%, 6.4% and 4% respectively which was comparable with the study of Gandhi et al5and Gupta et al.[17]

Majority of the smears (96.2%) were reported Negative for intraepithelial lesion or malignancy in the present study. The findings were comparable to

those observed by Gandhi et al,[5] Gupta et al,[17] Das et al,[19] Mulay et al[20] and Bhavani et al.[22] Majority of inflammatory smears were found in 31-40 years age group (38.8%) followed by 21-30 years age group (29.5%). The present study findings were comparable with the study of Gandhi et al,[5] Bhojani et al,[9] Sachan et al,[10] and Gupta et al.[17] Percentage of atrophic smear in the present study was 5.17%, these results are comparable with studies of Gandhi et al (5.3%)[5] and Mulay et al (6.9%).[20]

Although pap smear cytology is very economical and useful method for diagnosis of cervical pathology but unfortunately, many developing countries like Pakistan lack the facility to carry out widespread Pap screening.

CONCLUSION

A cost- effective screening method should be developed along with training of medical and paramedical staff in public as well private institutions. In Pakistan most of the patients belong to poor socioeconomic status and not aware of the importance of this screening program.

Organized screening with proper follow up and infrastructure improvement with the education about prevention is better than cure should be the first goal of screening with Pap to prevent the cervical cancer in the developing countries.

Limitations of Study

HPV is the main risk factor for development of cervical premalignant and malignant lesions. Pap smears should be subsequently followed with Human papilloma virus deoxyribonucleic acid (HPV-DNA) testing. This facility is available only at few centers

Authors' Contribution

NK: Substantial contribution to conception and design, acquisition of data, analysis and interpretation of data and drafting the article.

AA: Substantial contributions to cytological diagnosis of pap smears.

SK: Substantial contribution toanalysis and interpretation of data.

NWY: Drafting the article and revising it critically for important intellectual content.

Conflict of Interest: None.

Financial Disclosures: None.

Acknowledgement

The authors are grateful to laboratory staff from pathology department of Rashid Latif Medical College for their assistance.

REFERENCES

1. Arulponni TR, Janaki MG, Nirmala S, Ramesh BS, Rishi KS, Kirthi K. Carcinoma cervix treated with radiotherapy—our experience with emphasis on our concerns. IJOG. 2010 Feb;60(1):61-5.
2. Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. LANCET GLOB HEALTH. 2020 Feb; 8(2): e191-203.
3. Patel MM, Pandya AN, Modi J. Cervical Pap smear study and its utility in cancer screening, to specify the strategy for cervical cancer control. Nat J. Community Med. 2011;2(1):49-51.
4. Shaki O, Chakrabarty BK, Nagaraja N. A study on cervical cancer screening in asymptomatic women using Papanicolaou smear in a tertiary care hospital in an urban area of Mumbai, India. J Family Med Prim Care. 2018 Jul;7(4):652.
5. Gandhi SS, Shah PC. Utility of Papanicolaou's smears in the diagnosis of premalignant and malignant lesions of the cervix in a tertiary care centre of South Gujarat. Int J Res Med Sci. 2019 Sep;7:3342-51.
6. Suvarna KS, Layton C, Bancroft JD. Bancroft's theory and practice of histological techniques E-Book. Elsevier Health Sciences; 2018. Available online at: https://www.academia.edu/ 40252505/ Bancrofts_Theory_and_Practice_of_Histological_ Techniques
7. Nayar R, Wilbur D. The Bethesda System for Reporting Cervical Cytology. 3rd ed. Springer International Publishing; 2015.
8. Davey DD, Cox JT, Austin RM, Birdsong G, Colgan TJ, Howell LP, et al. Cervical cytology specimen adequacy: patient management guidelines and optimizing specimen collection. J Low Genit Tract Dis. 2008 Apr;12(2):71-81.
9. Bhojani KR, Garg R. Cytopathological study of

cervical smears and correlation of findings with risk factors. Int J Biol Med Res. 2011;2(3):757-61.

10. Sachan PL, Singh M, Patel ML, Sachan R. A study on cervical cancer screening using pap smear test and clinical correlation. Asia Pac J Oncol Nurs. 2018 Jul;5(3):337.
11. Chakraborty R, Chakraborty D, Majumder H. Detection Of Abnormal Cervical Cytology In Papanicolaou Smears At A Tertiary Care Hospital. IOSR J Dent Med Sci ;2016 Oct;15(10):20-4.
12. Manoli N, Manoli N, Kamath A, Kulkarni S. Recent Concepts in Cytology for Early Detection of Cervical Cancer. Cerv Cancer Recent Res Rev Stud. 2016;1-33.
13. Saha D, Ghosh S, Nath S, Islam H. Utility of pap smear screening for prevention of cervical cancer–A 3yrs study from rural Tripura–A northeastern state of India. Int J Med and Dent Sci. 2017;6(2):1456-61.
14. Bisht M, Agarwal S, Upadhyay D. Utility of Papanicolaou test in diagnosis of cervical lesions: a study in a tertiary care centre of western Uttar Pradesh. Int J Res Med Sci. 2015 May;3(5):1070.
15. Bal MS, Goyal R, Suri AK, Mohi MK. Detection of abnormal cervical cytology in Papanicolaou smears. J. Cytol. 2012 Jan;29(1):45.
16. Khattak ST, Naheed T, Akhtar S, Jamal T. Detection of abnormal cervical cytology by pap smears. Gomal J Med Sci. 2006;4(2):74-7.
17. Gupta K, Malik NP, Sharma VK, Verma N, Gupta A. Prevalence of cervical dysplasia in western Uttar Pradesh. J Cytol. 2013;30(4):257-62.
18. Kalyani R, Sharief N, Shariff S. A Study of Pap Smear in a Tertiary Hospital in South India. J Cancer Biol Res. 2016;4(3):1084.
19. Das D, Kar A, Rath S, Baliarsingh SK, Prusty D, Dash AK. Cytological pattern of papanicolaou smears and detection of cervical cancers: An experience from a tertiary care center of eastern zone of India. Oncol J India. 2018 Api;2(2):25.
20. Mulay K, Swain M, Patra S, Gowrishankar S. A comparative study of cervical smears in an urban Hospital in India and a population-based screening program in Mauritius. Indian J Pathol Microbiol. 2009 Jan;52(1):34–7.
21. Bajpai M, Raina A, Dwivedi S. A study of Pap smears in a tertiary care hospital: IOSR-JDMS, 2016 Feb;15(2):93-5.
22. Bhavani K, Vijaya Sheela P, Vani I, Uma N, Jyothsna Y. Study of cervical cytology in papanicolaou smears in a tertiary care center. Int Arch Integr Med. 2017 Nov;4(11):172-6.

VAGINAL BIRTH AFTER CAESAREAN SECTION

Nargis Iqbal,[1] Khulood Mukhtar,[2] Nazia Nawaz,[3] Mehreen Nisar,[4] Marriam Pervaiz Lali[5]

How to cite: Iqbal N, Mukhtar K, Nawaz N, Nisar M, Lali MP. Vaginal birth after caesarean section. JAIMC. 2021; 19(1): 103-106.

Abstract

Objectives: To determine the factors responsible for successful vaginal delivery after previous caesarean section.

Methodology: It was a prospective observational cohort conducted at department of Obstetric and Gynecology Unit 3 Jinnah hospital Lahore, a tertiary care teaching hospital, over a period of one year from First April 2017 to 31st March 2018 after approval from Institutional Ethical Committee. A total 150 pregnant women fulfilling the inclusion criteria were included in the study after informed consent.

Results: The mean age of the women was 24+_3.5 years. Successful VBAC was 76%, the commonest indication for repeat caesarean section was fetal distress 41.66%. Spontaneous onset of labour, previous VBAC, Bishop's score >5 and fetal weight 3 & <3 kg turned out to significant in fruitful VBAC.

Conclusions: Successful vaginal delivery after previous C/S of non-recurrent indication is possible and safe in selected women fulfilling the criteria of vaginal delivery.

Key words: Previous one LSCS, Trial of labour

Worldwide Caesarean delivery rates have increased markedly. In the United States, caesarean section (CS) rates enhanced from 5% to 31.9%.[1] Though many efforts were tried to decrease the rate of CS as recommended by WHO to 10%-15%, but in vain.[2] Repeat CS is the single most important contributory factor to raised CS rates.[3] Edwin Bradford Cragin, a famous Obstetrician quoted "Once a cesarean, always a cesarean" now this is being true.[4] National Institute of Health (NIH) and American Congress of Obstetrician and Gynecologists (ACOG) in 1980 supported "trial of labour" after CS (TOLAC), and this guided increase in vaginal birth after cesarean (VBAC) in developed countries.[5,6] Several national medical associations now have put up practical guidelines for normal vaginal delivery after CS[7] (VBAC) but these vary from country to country.[8] There are 60%-70% chance of low maternal morbidity in fruitful TOLAC than ERCD.[9,10] Every women for successful VBAC should be evaluated on the basis of complete history, clinical examination and investigations[11,12] maternal demographic predictors e.g age, height, weight and ethnicity play a significant role for fruitful VBAC.[13,14] Fifty to 75% chances of successful VBAC depend upon two main factors, size and type of maternal pelvis and estimated fetal weight.[9,10] In spite of all above mentioned factors woman preference, comfort and informed consent for TOLAC is also helpful.[9] The purpose of the study was to find out factors responsible for successful VBAC in uncomplicated booked women with previous LSCS.

1. Nargis Iqbal
2. Khulood Mukhtar
3. Nazia Nawaz
4. Mehreen Nisar
5. Marriam Pervaiz Lali

1-5. Department of Gynaecology, Al-Aleem Medical College/Gulab Devi Hospital, Lahore

Correspondence:
Dr. Nargis Iqbal, Department of Gynaecology, Al-Aleem Medical College/Gulab Devi Hospital, Lahore

Submission Date: 12-11-2020
1st Revision Date: 27-11-2020
Acceptance Date: 14-12-2020

METHODOLOGY

It was a prospective observational cohort conducted at department of Obstetric and Gynecology Unit 3 Jinnah hospital Lahore, a tertiary care teaching hospital, over a period of one year from First April 2017 to 31st March 2018 after approval from Institutional Ethical Committee. A total 150 pregnant women fulfilling the inclusion criteria were

included in the study after informed consent. Inclusion criteria: Booked or selected unbooked, previous LSCS due to non- recurrent cause, singleton pregnancy, pregnancy interval > 2 years, no medical or obstetrical complications during pregnancy, adequate pelvis and fetal weight <3.5 k.g, Exclusion criteria: Complicated unbooked, CPD, Medical or Obstetrical complication in current pregnancy, fetal weight > 3.5 k.g. Non probability convince sampling technique was used. Data like age, parity, indication for previous C/S, any operative complication in previous surgery, gestational age, history of previous VBAC, weight, height were recorded on pre designed proforma. After taking history a complete general physical, abdominal and pelvic examination were carried out. All the women were counseled regarding trial of labour either successful VBAC, or emergency caesarean section. All the data was entered and analyzed with the help of SPSS software version 16.

RESULTS

In this study the commonest age group of the women was 20 – 26 years and mean age was 24±3.5 years. Table I highlight the demographic data of women recruited in this study, and Table II spotlight the indication of previous C/S and successful VBAC or repeat emergency caesarean section in current pregnancy. Indications for repeat emergency caesarean in this study are enumerated in Table III and Table IV is mainly focused on the factors responsible for successful VBAC in our study.

Table 1: Demographic Data of the Women (n= 150)

Variables	No. of Women	Percentage
Age years		
20-25	112	74.66
26- 30	38	25.33
Parity		
G2 PI	67	44.66
G3 P2	45	30.oo
G4 or more	38	25.33
Booking Status		
Booked	125	83.33
Unbooked	25	16.6
Pregnancy Interval		
> 2 years	108	72
< 2 years	42	28

DISCUSSION

Table 2: Indication of Previous C/S & Current Outcome

Indications of Previous C/S	No of Cases (n=150)	Successful VBAC (n=114)(76.0)%	Emergency C/S (n=36)(24.0)%
Fetal Distress	51	41 (80.39)	10 (19.60)
Failed progress	29	21 (72.41)	8 (27.58)
Preg Induced HT	18	14 (77.77)	4 (22.22)
Failed Induction	13	9 (69.23)	4 (30.76)
Placenta Previa	11	8 (72.72)	3 (27.27)
Twin Pregnancy	9	7 (77.77)	2 (22.22)
Cervical dystocia	8	6 (75.00)	2 (25.00)
Mal Presentation	7	5 (71.42)	2 (28.57)
Reduced AFI	3	2 (66.66)	1 (33.33)
Cord Prolapse	1	1 (100.00)	

Table 3: Indication of Repeat Caesarean Section

Indication of Repeat C/S	No of Cases (n=36)	Percentage (24)
Fetal Distress	15	41.66
Failed progress	7	19.44
Scar tenderness	5	13.88
Malposition	5	13.88
Cervical dystocia	3	8.33
Maternal request	1	2.77

Caesarean Section is said to be the commonest performed surgical procedure in Obstetric Worldwide,[15] because of increasing rates of CS different proposals were given that trial of vaginal delivery after CS may be fruitful in reducing repeat CS.[16] The Obstetrician conducting VBAC is always in dilemma because of its forgoing complications. Every women must be carefully assessed in regard with possibility of successful VBAC. Vaginal delivery after CS (VBAC) is associated with short hospital

Table 4: Factors Responsible for Successful VBAC (n=150)

Factors	No of Women	Percentage
Age < 30 years	114	76.00
Previous Successful VBAC	118	78.66
Spontaneous Labour	120	80.oo
Pregnancy Interval>2Year	125	83.33
BMI < 25	125	83.33
Bishop Score > 5	130	86.66
Fetal Weight <_ 3 k.g	120	80.00

stay and prevention of complication from anesthesia and surgery.[17] The success of vaginal delivery after CS due to non-recurrent indications had been reported by different authors is 60%-80%,[18] but in our study the success was 76% which is correlating with other studies.[19,20] In the present study majority of women 74.66% were between 20-25 years of age reflecting the child bearing, 55.33% women were having parity more than one and 44.66% were second gravida with previous CS, these findings are tallying with other studies.[21,22] Major chunk of the women 83.33% were booked, inter pregnancy interval was more than 2 years in 72% and less than 2 years in 28% of women this is similar with other studies.[21,2] The success rate of VBAC in this study was 76% which is telling with other studies.[19,21,23] Table ll highlight the indications of previous C/S and current pregnancy outcome, In our study, the frequent indication of previous C/S was fetal distress the successful VBAC in this indication in our study was 80.39% which is mimic with other researchers.[21, 24] Table lll highlight the indication of repeat C/S, In the present study the rate of repeat C/S was 24% which is similar with other studies[22, 25] but quite high in respect with others researches.[21,26] The commonest indication was fetal distress found in 41.66%, similar with other studies.[21,25] Scar tenderness was observed in 13.88% in the current study all were managed by repeat C/S, but in 05.55% scar dehiscence were seen this is also found in other studies.[21,26] Factors responsible for successful VBAC in our study are mentioned in Table IV. Previous VBAC, and spontaneous onset of labour are said to be the good predictors for successful VBAC, in this study 78.66% had previous successful VBAC, and 80.00% women presented with spontaneous onset of labour this is similar with other studies.[17,27] The good Bishop score at the time admission is an important factor for the success rate of VBAC, in this study 86.66% the women have Bishop score >5, this is tallying with other studies.[21,22] Pregnancy interval and maternal BMI also play a contributory factors in the success of VBAC, if the pregnancy interval is more than 2 years outcome is better, in our study 83.33% women were having pregnancy interval more than 2 years who had successful VBAC, this finding is also observed in other studies.[21,28] Maternal BMI <25 is considered to be fair causative factor in fruitful VBAC, this is observed in 83.33% in the present study which is mimic with other studies[16,22]. Fetal weight is said to be a dominant predictor in the success rate of VBAC, the success decreased markedly (18.7) if fetal weight is more than 3 kg.[27] The fetal weight was 3 or less than 3 k.g in 80% of successful VBAC in our study and this is similar other studies.[29,30] There was no maternal and neonatal mortality in this study.

Limitations of the Study

The main limitations of this study is that as it was conducted in one of the tertiary care hospital where manpower is adequate for close vigilant monitoring of each VBAC to reduce complications.

CONCLUSIONS

Successful vaginal delivery after previous C/S of non-recurrent is possible in selected women fulfilling the criteria of vaginal delivery. The factors responsible for successful VBAC in our study were younger women, previous VBAC, spontaneous onset of labour, normal BMI, Good Bishop' s score and fetal weight 3 or <3 k.g.

REFERENCES

1. Joyce A, Martin MPH, Hamilton PD BE, Osterman MHS MUK. Births in the United States, 2016. NCHS Data Brief;2017;287:1-8.
2. World Health Organization Human Reproduction Program A, WHO statement on cesarean section rates. Reprod Health Matters,2015;23(45):149-50.
3. Cheng YW, Eden KB, Marshall N, Pereira L, Caughey AB, Guise JM. Delivery after prior cesarean: maternal morbidity and mortality. Clin Perinatol 2011;38(2):297-309.
4. Hibbard JU, Gilbert S, Landon MB, Hauth JC, et al. Trial of labour or repeat cesarean delivery in women with morbid obesity and previous cesarean delivery. Obtet Gynecol 2006;108(10:125-133.
5. National Institutes of Health state of the science

conference statement: Cesarean delivery on maternal request. Obstet Gynecol 2006;107(6):1386-1397.

6. American College of Obstetrician and Gynecologists, ACOG committee no.559:Cesarean delivery on maternal request. Obstet Gynecol 2013; 121(4): 904-7.
7. Bellows P, Shah U, Hawley L, Drexler K, et al. Evaluation of outcomes associated with trial of labour after cesarean delivery after a change in clinical practice guidelines in an academic hospital. J Matern Fetal Neonatal Med.2017;30(17):2092-6.
8. Foureur M, Ryan CL, Nicholl M, Homer C. Inconsistent evidence: analysis of six national guidelines for vaginal birth after cesarean section. Birth 2010; 37(1):3-10.
9. Fagerberg MC, Marsal K, Kallen K. Predicting the chance of vaginal delivery after one cesarean section: validation and elaboration of a published prediction model. Eur J Obstet Gynecol Reprod Biol 2015;188:88-94.
10. Miller ES, Grobman WA. Obstetric outcomes associated with of labour after 2 prior cesarean deliveries. Am J Obstet Gynecol 2015;213(1):85-89.
11. Grantz KL, Gonzalez QV, Troendle J, Reddy UM, et al. Labour patterns in women attempting vaginal birth after cesarean with normal neonatal outcomes. Am J Obstet Gynecol 2015; 213(2):220-26.
12. Senturk MB, Cakmak Y, Atac H, Budak MS. Factors associated with successful vaginal birth after cesarean section and outcomes in rural area of Anatolia. Int J Womens Health 2015;7:693-97.
13. Carroll CS Sr, Magann EF, Chauhan SP, Klauser CK, Morrison JC. Vaginal birth after cesarean section versus elective repeat cesarean delivery: Weight-based outcomes. Am J Obstet Gynecol 2013;188(6) 1516-20.
14. Knight HE, Gurol-Urganci I, Van der Meulen JH, Mahmood TA, et al. Vaginal birth after cesarean section: a cohort study investing factors associated with its uptake and success. BJOG 2014; 121(2): 183-92.
15. American College of Obstetrician and Gynecology (ACOG). ACOG Practice Bulletin: Vaginal birth after previous caesarean delivery: Clinical management guidelines. Int J Gynecol Obstet. 2004;54:197-204.
16. Shadi Rezai, Meghan Labine, Sri Gottimukkala, Steven Karp, Lesly Sainvil, Guy Isidore. Trial of Labour after Caesarean for Vaginal Birth after Previous Caesarean section Versus Repeat Caesarean; A review. Obstet Gynecology Int J 2016; 4(6): 00135.
17. Birara M, Gebrehiwot Y. Factors associated with success of vaginal birth after one caesarean section (VBAC) at three teaching hospitals in Addis Ababa, Ethiopia: a case control study. BMC Pregnancy Childbirth 2013;13:31-35.
18. Royal College of Obstetricians and Gynecologists. Birth after previous caesarean section. Green top guideline No 45, RCOG press. Feb 2007.
19. Vidyadhar B. Bangal, Satyajit G, Vishesha Y, Kunal A, Dhruval B. Vaginal birth after cesarean section: Why and how? Int. J Repro Contraception, Obstet Gyne.2017;6(12):5554-5558.
20. Islam A, Ehsan A, Arif S, Murtaza J, Hanif A. Evaluating trial of scar in patients with a history of caesarean section. N Am J Med Sci 2011;3:201-205.
21. Vidyadhar B. Bangal, Purushottam A G, Kunaal K S, Satyajit P G. Vaginal Birth after Caesarean Section. N Am J Med Sci 2013;5(2):140-144.
22. Benish R, Iqbal N, Khan M S, Khan A M, Dastgir G. et al. Success Rate of Vaginal Deliveries after previous C-section in a Tertiary Care Hospital. PJMHS 2018;12(2):551-554.
23. Taj G, Sohail N, Cheema SZ, Zahid N. Review of study of study of vaginal birth after caesarean section. Annals of Surgery 2008;14(1):13-16.
24. Narang H, Singhal S, Ravi V. Assessment of factors individually and as a scoring system in predictive screening for VBAC in patients undergoing trial of labour after single previous cesarean section. IOSR-JDMS 2014; 13(10):109-15.
25. Malik U, Ishtiaq S, Baloch A. Frequency and safety of successful vaginal birth after previous single caesarean section. Isra Med J 2016;4:253-256.
26. Dayal V. Trial of vaginal delivery in cases of single previous caesarean section. J Obstet Gynecol 2005; 35: 445-450.
27. Landon MB, Leindecker S, Spong CY, Hauth JC, Bloom S, et.al. The MFMU caesarean registry: Factors affecting the success of trial of labour after previous caesarean delivery. Am J Obstet Gynecol 2005; 193:1016-23.
28. Shipp TD, Zelop CM, Repke JT, Cohen A, Lieberman E. Interdelivery interval and risk of symp-tomatic uterine rupture. Obstet Gynecol 2001; 97: 175-180.
29. Whiteside DC, Mahan CS, Cook JC. Factors associated with successful vaginal delivery after caesarean section. J Reprod Med 1983;28:785-788.
30. Senturk MB, Cakmak Y, Atac H, Budak MS. Factors associated with successful vaginal birth after caesarean section and outcomes in rural area of Anatolia. Int J Womens Health 2015;7:693-697.

NLR, PLR AND CRP AS PREDICTIVE INDICATORS TO DETERMINE THE SEVERITY AND PROGNOSIS OF COVID-19 PATIENTS AT JINNAH HOSPITAL, LAHORE, PAKISTAN

Saadat Ullah,[1] Muhammad Aleem,[2] Rabia Arshad,[3] Faiza Muzahir,[4] Subhan Saeed,[5] Emaan Salam,[6] Tanvir us Salam[7]

How to cite: Ullah S, Aleem M, Arsah R, Muzahir F, Saeed S, Salam E, et al. NLR, PLR and CRP as predictive indicators to determine the severity and prognosis of COVID-19 patients at Jinnah Hospital, Lahore, Pakistan. JAIMC. 2021; 19(1): 107-112.

Abstract

Background: The length of stay at hospital, severity, prognosis and mortality of COVID-19 patients depends on multiple factors. Since the start of the COVID 19 pandemic different prognostic markers are under investigation.

Objective: To determine theeffect of white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP) on severity and prognosis of COVID-19.

Methodology: Present descriptive cross-sectional study was being conducted at Jinnah hospital, Lahore. COVID-19 confirmed 100 patients were included in the present study as per inclusion/exclusion criteria. Demographic details were recorded and all patients were advised WBC, NLR, PLR and CRP. Descriptive statistics were applied to find the association of these biomarkers with COVID-19.

Results: 100 COVID-19 confirmed patients were enrolled (Male 55, Female 45) with a mean age of 52.34 ± 15.12 years. According to the severity, 16 % (N = 16) patients were mild (mean age 47.23 ± 16.11 years), 26 % (N = 26) were moderate (mean age 46.90 ± 15.34 years), 37 % (N = 37) patients were severe (mean age 54.33 ± 15.78 years), and 21% (N = 21) patients were critical (mean age 57.15 ± 15.54 years). The age, WBC, NLR, PLR and CRP were significantly higher in severe patients as compared to the non-severe subjects. The elevated levels of NLR (CI 9.1-5.233), and C-reactive protein (CI 0.524-0.9345) were found to be independent factors linked with COVID-19 progression.

Conclusion: NLR, PLR, CRP are reliable predictor marker to access the severity of COVID 19 disease and may help clinicians to identify high-risk COVID 19 patients at a primitive stage.

Keywords: WBC; NLR; CRP; PLR; COVID-19.

COVID-19 pandemic began in late 2019 in Wuhan, China, and has now targeted millions of people.[1] The COVID-19 was firstdocumented in Pakistan in February 2020 and it was declared as a global threat by WHO in March 2020.[2,3] In Pakistan, the total cases of COVID-19 by 15 August 2020 was 289,215 and total deaths were 6,175.2 Mortality of COVID-19 illness varies from country to country and is usually dependent on multiple factors.[4,5]

The clinical picture of COVID-19 subjects varies from asymptomatic to acute respiratory arrest, and multiple organ failure.[5] The COVID-19 illness is caused by a type of corona-virus which is known as SARS-CoV-2.[6] This SARS-COV-2 virus is now well known to cause respiratory failure and multiple organ failure.[7] These pulmonary and extra-pulmonary manifestations are usually caused by the underlying mechanism of attachment of SARS-COV-2 virus to Angiotensin-Converting Enzyme-2 (ACE2)

1. Saadat Ullah
2. Muhammad Aleem
3. Rabia Arshad
4. Faiza Muzahir
5. Subhan Saeed
6. Emaan Salam
7. Tanvir us Salam

1,3. Medical Unit 1 Jinnah Hospital Lahore
2. Endocrinology Fellow, Jinnah Hospital Lahore
4. Department of Nephrology, Jinnah Hospital Lahore
5,6. House Officer, Jinnah Hospital Lahore
7. Medical Unit I, Jinnah Hospital Lahore

Correspondence:

Submission Date: 12-10-2020
1st Revision Date: 18-11-2020
2nd Revision Date: 26-11-2020
Acceptance Date: 30-11-2020

receptors, present on multiple organs of human system including liver, lungs, heart, brain.[8,9]

The compromised immune system is usually the result of a severe inflammatory response to attacking the SARS-COV-2 virus.[9] This immune response usually results in a release of various inflammatory biomarkers in the bloodstream, and these potential circulating biomarkers can be used for monitoring the severity of COVID-19 disease.[10-12]

The collection of laboratory data about circulating inflammatory markers such as WBC, NLR, PLR, D-dimer, ferritin and CRP in COVID-19 confirmed patients can be used to determine their effect on progression and severity of COVID-19 patients.[13] The role of NLR and PLR is already established in various immune disorders because of ongoing inflammatory reactions.[13] Because of the contagious and hazardous nature of the virus, it is necessary to identify evidence of virus triggered inflammatory markers associated with disease mortality so that risk factors can be reduced associated with disease mortality.[14,15] Therefore, following this rationale, the aim of this research was to determine the effect WBCs, NLR, PLR and CRPon the severity and prognosis of COVID-19 patients admitted at HDU of Jinnah hospital, Lahore.

METHODOLOGY

A present descriptive cross-sectionalstudy was conducted at COVID HDU, Jinnah Hospital/AIMC, Lahore, over 45 days(from 20 June 2020 to 3 August 2020). The study was carried out after taking informed consent and ethical approval. A total of 100 COVID-19 patients were included and the sampling technique was non-probability consecutive sampling. Selection Criteria for the study includes

- COVID-19 confirmed patients as per WHO interim guidance& meeting the following criteria: Epidemiological history, (b) Fever or other pulmonary symptoms, (c) Typical chest X-ray appearance, and (d) RT-PCR + for SARS-CoV-2.[15]
- Willing to take part in the research.

Hundred COVID-19 confirmed patients were selec-ted in this cross-sectional study. All patients were advised WBC, NLR, PLR and CRP. Patients were classified into mild, moderate, severe, and critical groupsbased on the severity classification of COVID -19 patients issued by NHSRC, the government of Pakistan. The mild and moderate patients were taken as non-severe patients and they were those patients who met all following criteria: - (a) Epidemiological history, (b) Fever or other pulmonary symptoms, (c) Typical chest X-ray appearance, and (d) RT-PCR + for SARS-CoV-2.[15] Demographic details were recor-ded using pre-tested specially designed proforma. Age, gender, exposure history, comorbidities, length of hospital stay, mortality, chest radiograph findings, clinical sign/symptoms, and above-mentioned labo-ratory investigation findings were also recorded.

Quantitative datawere presented by mean ± SD & will be compared using Wilcoxon sum test. Qualitative data were presented by frequency and percentages & will be compared using Fisher exact and Chi-square test. 95% confidence interval (CI) was used to find out relative risk and enter elimination binary logistic regression analysis was run to find out the effect of age, sex, and all other variables on clinical course and outcome. A P ≤0.05 will be considered significant.

RESULTS

100 COVID-19 confirmed patients were enrolled (Male 55%, Female 45%) with mean age of 52.34 ± 15.12 years (Table 1). According to the severity (Figure 1), 16 % (N = 16) patients were mild (mean age 47.23 ± 16.11years), 26 % (N = 26) were moderate (mean age 46.90 ± 15.34years), 37 % (N = 37) patients were severe (mean age 54.33 ± 15.78 years), and 21% (N = 21) patients were critical (mean age 57.15 ± 15.54years). Although the mean age (p = 0.001), contact history (p=0.345), and co-morbidities (p=0.002)of severe patients were significantly higher but there are insignificant differences in terms of gender (p = 0.432), exposure (p = 0.345), symptom variation and length of hospital stay (p = 0.433) between severe and non-severe patients. (Table 1).

The fever (79%) and coughing (61%) were the most frequent symptoms. The mortality rate was 3%.

The age, WBC, NLR, PLR, and CRP of severe patients were significantly higher compared to the non-severe subjects (Table 1). The elevated levels of NLR(CI 9.1-5.233), and C-reactive protein (CI 0.524-0.9345) were found to be independent factors linked with COVID-19 progression identified by multivariate Cox regression. Enter elimination binary logistic regression analysis found that NLR and CRP were significantly linked with the risk of COVID-19. The predominant feature on chest radiograph for severe patients was diffuse lung infiltration while the predominant feature for non-severe patients was a normal appearance to peripheral lung involvement. Figure 2 showing results of receiver operating curve analysis to show optimum cut-off values of variables for differentiating severe from non-severe cases. The optimum cut-off values of NLR, PLR, age, WBC count, and CRP were 4.1, 191, 51.3 years, 8.1E9/L, and 27.2 mg/L, respectively.

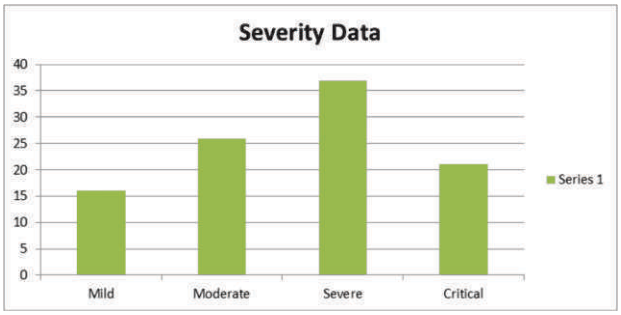


Figure1: *Distribution of Patient according to Severity*

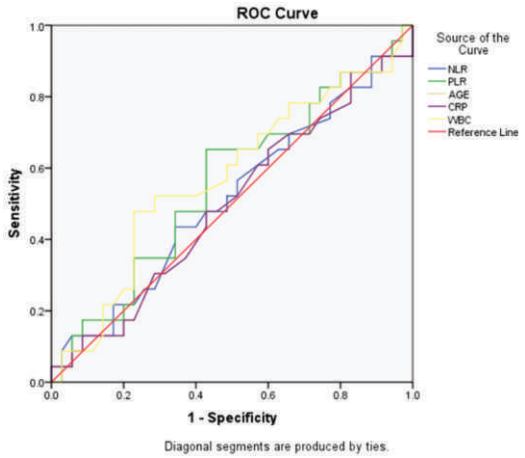


Figure 2: *ROC*

Table 1: *Comparison of Lab Investigations*

Variable	Severe % (N)	Non-Severe % (N)	Total % (N)	p-value
Age	57.34 ± 16.45	41.45 ± 14.12	52.34 ± 15.12	0.001
Gender (Male/Female)	32/26	23/19	55/45	0.432
BMI (kg/m²)	26	25	25± 3	0.532
Smoking	3	3	6 (6%)	0.125
Positive contact history	17	20	36 (36)	0.345
Co-morbidities				
No Co-morbidities	10	7	16	
Diabetes Mellitus	27	15	42	
Hypertension	24	11	35	0.003
Ischemic Heart Disease	10	3	13	
Others	14	5	19	
Length of Hospital Stay	29.7 ± 12.2 days	28.3 ± 11.3 days	28.2 ± 12.2 days	0.433
Mortality	3	0	3	0.007
Predominant Chest X-ray				
Peripheral involvement	22	25	47	
Peripheral & Basal	15	7	22	0.754
Diffuse infiltration	35	2	37	
WBC (Mean ±SD)	10.34 (± 3.13)	6.54 (± 3.22)	9.68 (±4.12)	<0.001
Lymphocytes	0.76 (± 0.12)	1.31 (± 0.60)	1.60 (±0.45)	<0.001
Neutrophils	7.56 (± 4.91)	4.23 (±0.23)	5.75 (±3.34)	<0.001
NLR (Mean ±SD)	16.90 (± 15.34)	4.11 (±3.33)	6.07 (±7.23)	<0.001
PLR (Mean ±SD)	257.56 (± 156.33)	101.07 (±65.11)	189.75 (±167.11)	<0.001
CRP (mg/L) (Mean ±SD)	61.11 (± 47.11)	19.23 (±21.23)	45.75 (±38.34)	<0.001

DISCUSSION

The limited studies are available regarding the effect of WBC, NLR, PLR and CRP on the severity and prognosis of COVID-19 patients. Therefore, the aim was to determine the effect of WBC, NLR, PLR and CRP on the severity and prognosis of COVID-19 patients admitted at HDU and ICU of Jinnah hospital, Lahore. The role of NLR as a biomarker is already proven in several inflammatory and immune-related conditions.16-19The NLR and PLR can easily be determined from serum CBC.

The results of the present study found that COVID-19 males were more in number than COVID-19 females, this is parallel with the results of previously conducted studies in China and elsewhere which showed that COVID-19 males were more in number than COVID-19 females.[20,21] The mean age of selected patients was 52.34 ± 15.12 Years, this is also parallel with the results of previously conducted studies where the mean age of selected COVID-19 patients was approximately 50 years,[20-23] however, this is different from the findings of a previously conducted study in France, where the mean age of selected COVID-19 patients was approximately 45 years.[24] The results also showed that the majority of the patients were in the severe group (58%) as compared to the non-severe patients (42 %), however, this is different from the findings of previously conducted studies, where a majority of the patients were non-severe.[21,25] The fever (79%) and cough (61%) were the most frequent symptoms, this is in line with the findings of previously conducted studies.[26,27]

The age, WBC, NLR, PLR, and CRP of severe patients were significantly higher in severe subjects. The elevated levels of NLR and CRP were found to be independent factors linked with COVID-19 progression. This is in line with the results of recently conducted studies.[14-16] The increased levels of CRP and NLR in the bloodstream in severe patients can be linked to the instant migration and activation of T cells from the venous system to immune organs; this can also be linked to the antibody-dependent cell-mediated reaction in response to viral attack, and due to the release of virus-related inflammatory factors produced by vascular cells.[15] As the COVID-19 virus infect T cells of the immune system via ACE-2 receptors and glycoprotein, this results in a decrease in levels of lymphocytes and inflammatory cytokines, which eventually results in death and multiple organ failure via cytokine storm.[15]

Limitations of Study

There are several limitation of the study including small sample size, single-centric research, and need for follow-ups of these biomarkers at longer time periods. It is still unknown that to what extent and accuracy, these biomarkers would do a risk assessment of COVID-19 patients. Further large-scale studies with longer follow-up periods are suggested.

This study has high number of severe and critical patients because those with mild and moderate disease with no comorbidities were advised home isolation and observation.

However, within these limitations, the result showed that levels of NLR and CRP were highly related to a course of COVID-19 illness.

There are great clinical implications of this study for third world countries like Pakistan as NLR can easily be determined using serum CBC using differential count and is a cost-effective laboratory investigation

CONCLUSION

The age, WBCs and PLR were significantly higher in severe patients as compared to non-severe patients. Immune inflammatory parameters like NLR, PLR, and CRP were associated with the severity and prognosis of the disease. These may be rapid, cost beneficial and auspicious markers to assist in diagnosis, risk assessment, and predicting the severity of the disease. With the assistance of these biochemical markers, we can prioritize treatment guides and stratify patients for preliminary management.

Acknowledgment

Prof Dr Tanveer us Salam, Head Medical Unit 1

Conflict of Interest: None

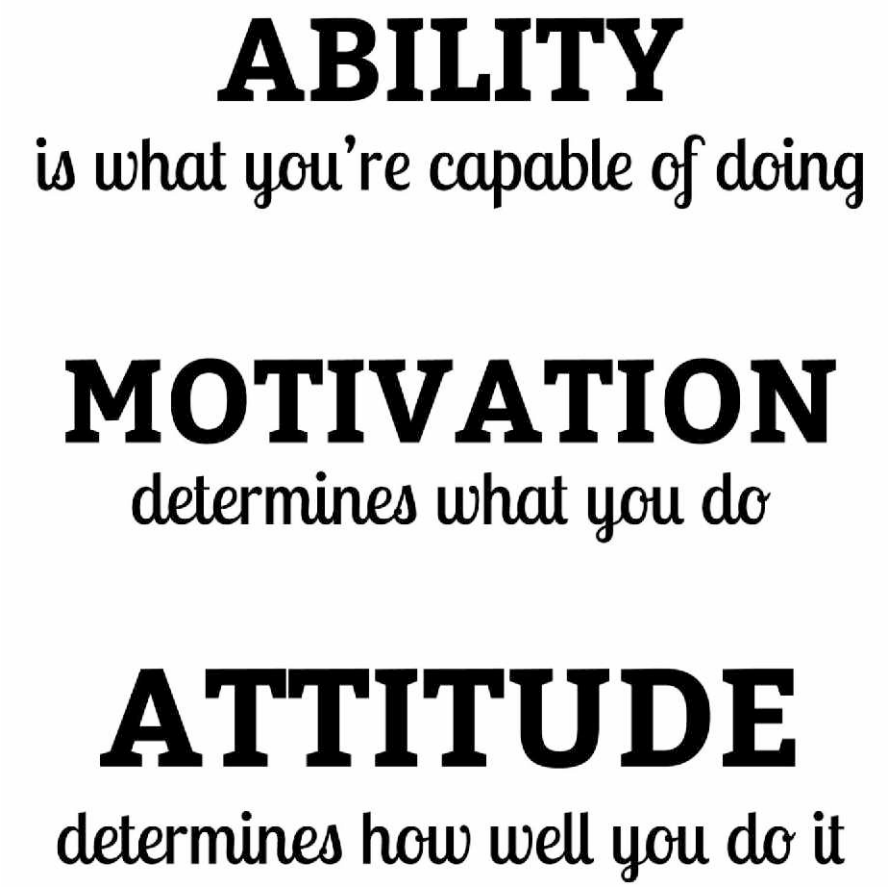
Fundinng: None

REFERENCES

1. Zhang Y, Ma ZF: Impact of the COVID-19 pandemic on mental health and quality of life among local residents in Liaoning Province, China: A cross-sectional study. International journal of environmental research and public health. 2020, 17:2381.
2. Khan S, Khan M, Maqsood K, Hussain T, Zeeshan M: Is Pakistan prepared for the COVID-19 epidemic? A questionnaire-based survey. Journal of Medical Virology. 2020.
3. Cucinotta D, Vanelli M: WHO declares COVID-19 a pandemic. Acta bio-medica: Atenei Parmensis. 2020, 91:157-160.
4. Ji Y, Ma Z, Peppelenbosch MP, Pan Q: Potential association between COVID-19 mortality and health-care resource availability. The Lancet Global Health. 2020, 8:e480.
5. Wu X, Nethery RC, Sabath BM, Braun D, Dominici F: Exposure to air pollution and COVID-19 mortality in the United States. medRxiv. 2020.
6. Porcheddu R, Serra C, Kelvin D, Kelvin N, Rubino S: Similarity in case fatality rates (CFR) of COVID-19/SARS-COV-2 in Italy and China. The Journal of Infection in Developing Countries. 2020, 14:125-128.
7. Ahmed SF, Quadeer AA, McKay MR: Preliminary identification of potential vaccine targets for the COVID-19 coronavirus (SARS-CoV-2) based on SARS-CoV immunological studies. Viruses. 2020, 12:254.
8. Cheng H, Wang Y, Wang GQ: Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. Journal of medical virology. 2020.
9. Tolouian R, Vahed SZ, Ghiyasvand S, Tolouian A, Ardalan M: COVID-19 interactions with angiotensin-converting enzyme 2 (ACE2) and the kinin system; looking at a potential treatment. Journal of Renal Injury Prevention. 2020, 9:e19-e19.
10. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A: The role of biomarkers in diagnosis of COVID-19-A systematic review. Life Sciences. 2020: 117788.
11. Montesarchio V, Parella R, Iommelli C, Bianco A, Manzillo E, Fraganza F, Palumbo C, Rea G, Murino P, De Rosa R: Outcomes and biomarker analyses among patients with COVID-19 treated with interleukin 6 (IL-6) receptor antagonist sarilumab at a single institution in Italy. Journal for immunotherapy of cancer. 2020, 8.
12. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, Jiang X, Li X: C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. Journal of Medical Virology. 2020.
13. Assandri R, Buscarini E, Canetta C, Scartabellati A, Viganò G, Montanelli A: Laboratory Biomarkers predicting COVID-19 severity in the Emergency room. Archives of medical research. 2020, 51:598-599.
14. Sahu BR, Kampa RK, Padhi A, Panda AK: C-reactive protein: a promising biomarker for poor prognosis in COVID-19 infection. Clinica Chimica Acta. 2020.
15. Yang A-P, Liu J, Tao W, Li H-m: The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. International immunopharmacology. 2020:106504.
16. Ying H-Q, Deng Q-W, He B-S, Pan Y-Q, Wang F, Sun H-L, Chen J, Liu X, Wang S-K: The prognostic value of preoperative NLR, d-NLR, PLR and LMR for predicting clinical outcome in surgical colorectal cancer patients. Medical oncology. 2014, 31:305.
17. Uslu AU, Küçük A, Şahin A, Ugan Y, Yılmaz R, Güngör T, Bağcacı S, Küçükşen S: Two new inflammatory markers associated with Disease Activity Score-28 in patients with rheumatoid arthritis: neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. International journal of rheumatic diseases. 2015, 18:731-735.
18. Saeed A, Rosati L, Narang A, Moningi S, Hacker-Prietz A, Le D, Zheng L, Laheru D, Ellsworth S, Herman J: Elevated Absolute Monocyte Count, Absolute Neutrophil Count, and Neutrophil-to-Lymphocyte Ratio as Prognostic Factors in Locally Advanced Pancreatic Cancer Patients Treated With Stereotactic Body Radiation Therapy. International Journal of Radiation Oncology• Biology• Physics. 2015, 93:E157.
19. Shimoyama Y, Umegaki O, Inoue S, Agui T, Kadono N, Minami T: The Neutrophil to Lymphocyte Ratio Is Superior to Other Inflammation-Based Prognostic Scores in Predicting the Mortality of Patients with Pneumonia. Acta Medica Okayama. 2018, 72:591-593.
20. Ahmed M, Umar M, Sufyan A, Zeb S, Ahmad H, Shahid R: Liver Function Tests; a Marker of

Severity in Covid 19 Patients. Austin Hepatol. 2020, 5:1013.

21. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020, 395:497-506.
22. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, Fan Y, Zheng C: Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. The Lancet Infectious Diseases. 2020.
23. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L: Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology. 2020: 200642.
24. Gautret P, Lagier J-C, Parola P, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Dupont HT: Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International journal of antimicrobial agents. 2020:105949.
25. Guan W-j, Liang W-h, Zhao Y, Liang H-r, Chen Z-s, Li Y-m, Liu X-q, Chen R-c, Tang C-l, Wang T: Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. European Respiratory Journal. 2020, 55.
26. Lu H, Stratton CW, Tang YW: Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. Journal of medical virology. 2020, 92:401-402.
27. Hui DS, Azhar EI, Madani TA, Ntoumi F, Kock R, Dar O, Ippolito G, Mchugh TD, Memish ZA, Drosten C: The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—The latest 2019 novel coronavirus outbreak in Wuhan, China. International Journal of Infectious Diseases. 2020, 91:264-266.



ORAL HYGIENE AWARENESS IN PATIENTS VISITING PUBLIC & PRIVATE HEALTH FACILITIES OF PAKISTAN - A CROSS-SECTIONAL SURVEY

Asma Shakoor,[1] Benish Mehmood,[2] Sadia Rana,[3] Aleshba Saba Khan,[4] Yousaf Jamil,[5] Aleeza Sana[6]

How to cite: Shakoor A, Mehmood B, Rana S, Khan AS, Jamil Y, Sana A. Oral hygiene awareness in patients visiting public & private health facilities of Pakistan- a cross-sectional survey. JAIMC. 2021; 19 (1): 113-117.

Abstract

Objective: To determine the relationship between oral hygiene awareness & dental outcome & to find out the difference in oral health of patients visiting public & private health centers.

Methodology: In this cross-sectional survey 1787 patients visiting public and private health facilities of Islamabad, Pakistan were examined for their oral health assessment using WHO Oral health assessment forms. Non-probability convenient sampling method was employed. The subjects aged between 16 to 60 years were included in the study. Decayed Missing filled Teeth Index was used for caries status and Simplified Oral Hygiene Index was used for assessment of oral health. To determine the awareness regarding oral hygiene few close ended questions were asked. Patients with smoking, betel nut and alcohol consumption were excluded from the study. The data was entered and analyzed using SPSS version 25.

Results: In this study 1122 (62.8%) participants were male and 665 (37.2%) were female. Only 524 (46.7%) males and 221 (33.2%) females reported brushing their teeth twice daily. As far as dental visits were concerned, 471 (42.0%) males and 346 (52.0%) females reported that they never visited a dentist before. Overall 371 (20.8%) participants had good awareness, 802 (44.9%) had moderate and 614 (34.4%) had low oral hygiene awareness.

Conclusions: In general population there is average awareness level regarding oral hygiene. It is highly recommended to organize health education camps to educate public regarding oral hygiene. Oral hygiene practices among common people needs improvement.

Key words: Oral Hygiene, Adult Patients, Public and Private Health Facilities

Mouth is gate way to good general health. According to World Health survey 2017, Oral diseases are contributing in global disease burden like other non-communicable diseases and they are considered as a major public health concern due to their effect on one's quality of life.[1] On the other hand, dental treatment is expensive and in most of the countries universal health coverage facility is not available.[2] In such scenario prevention is consi-dered better rather cure. Research studies previously conducted in Pakistan revealed that the brushing/ Maswak usage is common among population but the cleaning aid like flossing and mouth wash usage is not practiced. Similarly, the patients prefer self-medication rather than visiting the dentist.[3,4]

Pakistan is a developing country and in develo-ping countries the improving economic condition/ urbanization has contribution in oral health.[5] Dental caries, periodontal disease and oral cancer are most common oral ailments globally.[6,7] Dental caries and

1. Asma Shakoor
2. Benish Mehmood
3. Sadia Rana
4. Aleshba Saba Khan
5. Yousaf Jamil
6. Aleeza Sana

1,2. Community & Preventive Dentistry Department, Army Medical College, Rawalpindi (NUMS)
3. Oral Biology Department Sharif Medical and Dental College,Lahore
4. Department of Prosthodontics, Islamabad Medical and Dental College.
5. Oral Biology Department Rawal Institute of Health Sciences,Islamabad
6. General Dental Practitioners

Correspondence:
Dr. Asma Shakoor, *Associate Professor, Community & Preventive Dentistry Department, Institute of Dentistry,CMH-Lahore Medical College, (NUMS), Email: asmashakoor@hotmail.com*

Submission Date: 10-10-2020
1st Revision Date: 15-11-2020
Acceptance Date: 22-11-2020

periodontal diseases lead to other oral manifestations. Literature reveals that the leading cause of tooth extraction in younger age was dental caries followed by periodontal disease.[8,9] On the other hand it was found that dental caries was inversely related with socio-economic status.[10] High sugar consumption, fast food intake, smoking and alcohol consumption are leading causes of poor dental health. Research studies have shown an association between periodontal disease and obesity.[11] Some other studies have documented the contributing role of poor oral hygiene with respiratory and gastric disease.[12]

Many studies have been conducted to determine oral health awareness of general population. But these studies were simple descriptive studies. The current study is aimed to determine the relationship between oral hygiene awareness & dental outcome and secondly, to find out the difference in oral health of patients visiting public and private health centers.

METHODOLOGY

After seeking permission from the respective health care centers, informed consent was obtained from every patient. Confidentiality of data was ensured. This cross-sectional survey was conducted from the period of March 2019 to July 2019. Total 1787 patients visiting private and tertiary health care setup of Islamabad city were examined. WHO Oral health assessment forms were used for assessment of Oral hygiene status of patients. The study was conformed to STROBE guidelines for cross sectional studies.[13] The data was collected on the basis of researcher's convenience therefore non-probability convenience sampling technique was used. Both males and females aged between sixteen to sixty years were included in the study. Patients consuming alcohol or betel nut and smokers were excluded from the study.

Patients attending Dental Outpatient department with different oral health issues were examined by trained dental surgeons. Mouth mirror and explorer were used for examination. No radiographs were taken. The assessment form comprised of different sections. First section contained demographic information of patients including age, gender, occupation, ethnic background, frequency of dental visits, frequency of tooth brushing, use of oral hygiene aids like etc. In second section, dentition status was recorded using Decayed, Missing, Filled teeth Index (DMFT). To check oral hygiene status of the patients, Simplified Oral Hygiene Index (OHI-S) was used. OHI-S Index has 2 components, Calculus Index-Simplified & Debris Index-Simplified. By summing up these 2 components, OHI-S is obtained for an individual. This index is interpreted as: 0 to 1.2---good, 1.3 to 3.0---fair, and 3.0 to 6.0---poor.

To determine the awareness regarding oral hygiene following close ended questions were asked "how often do you brush your teeth", "how often do you visit dentist", "how do you move brushing on your teeth", "do you think the only remedy for toothache is removing the tooth" etc. Correct response rate less than 50% was considered as low awareness, 50% to 80% was considered as moderate and above 80% was considered as good awareness. Chi square test was applied to determine the association between study variable and awareness/visiting facility type i.e. Public or Private teaching hospital. P-value of less than 0.05 was considered as significant.

Treatment need was also selected according to WHO intervention urgency. There were 5 categories. Score 0 indicated that no treatment was required for the patient, Code 1 was for preventive or routine treatment, Code 2 was assigned to those patients who required prompt treatment including scaling, Code 3 was for urgent or immediate treatment need and Code 4 indicated referral for comprehensive evaluation.

RESULTS

Total 1787 patients participated in this study, out of which, 1122 (62.8%) were males and 665 (37.2%) were females. Mean age of the patients was 45.18±12.26 years, ranged between 16 to 60 years. Among the patients 615 (34.4%) had no decayed,

missing or filled teeth. Mean DMFT score was 2.27± 2.47. Regarding Oral hygiene, 597 (33.4%) participants had excellent, 470 (26.3%) had good, 479 (26.8%) had fair and 241 (13.5%) had poor oral hygiene. As far as oral hygiene awareness is concerned, 371 (20.8%) patients had good awareness, 802 (44.9%) had moderate and 614 (34.4%) had low oral hygiene awareness.

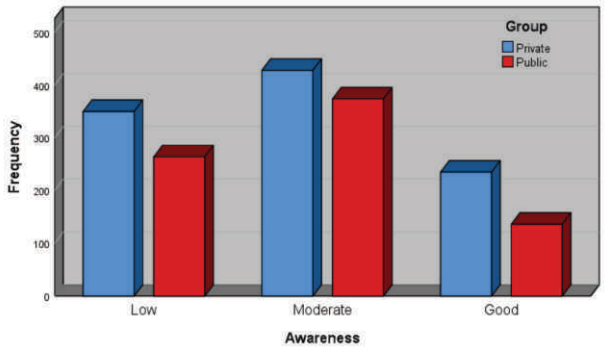


Figure 1: *Comparison of Awareness of Oral Hygiene among Patients Visiting Public and Private Teaching Hospitals*

Among the patients visiting private teaching hospital 350 (34.6%) had low, 428 (42.3%) had moderate and 235 (23.2%) had good awareness level. Among the tertiary health setup visitors, 264 (34.1%) had low, 374 (48.3%) had moderate and 136 (17.6%) had good awareness about oral hygiene (Figure 1). Statistically significant difference was found between awareness of patients visiting public and private teaching hospital.

Among low awareness group, 68 (32.4 %) patients didn't require any treatment, preventive treatment was needed in 216 (29.6%), Prompt treatment including scaling was required in 280 (37.8%), Immediate treatment was needed in 42(46.7%) and 8 (47.1%) required referral for comprehensive evaluation. In moderate awareness group, 91(43.3%) needed no treatment, 349 (47.9%) needed preventive treatment, 325(43.9%) needed prompt treatment including scaling, 32 (35.6%) required immediate treatment and 5(29.34%) were referred for comprehensive evaluation. Similarly, in patients with good awareness 51(24.3%) did not required any treatment, 164 (22.5%) required preventive treatment, 136 (18.4%) required prompt treatment including scaling, 16(17.8%) required immediate treatment and 4(23.5%) were referred for comprehensive evaluation (Figure 2). There was statistically significant association between awareness level and intervention urgency.

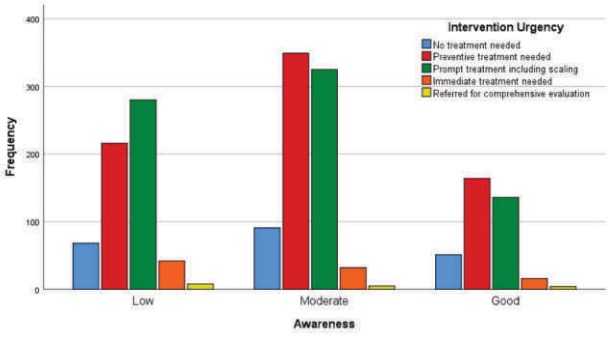


Figure 2: *Comparison of Intervention Urgency Regarding Awareness Level of Patients*

It was observed in the present study that public health facility was visited more by male patients as compared to females. Regarding brushing frequency, 524 (46.7%) males and 221(33.2%) females reported brushing their teeth twice daily. Similarly, 471(42.0%) males and 346(52.0%) females reported that they never visited a dentist before. Among patients visiting Private teaching hospitals, 946 (93.4 %) had no signs of dental injury as compared to patients visiting public hospital 753 (97.4%). The difference was statically significant (p-value <0.001) (Table 1).

Similarly, among patients visiting private hospital, 130 (12.8%) required no dental treatment as compared to 80 (10.3%) patients visiting public hospital. The difference in frequency of public and private patients regarding urgency of treatment was statistically significant (p-value <0.001). In present study, patients visiting hospital facility were statistically significantly and association was found with Dentist Visit, Brushing Frequency, Trauma and Intervention Urgency (Table 1)

DISCUSSION

In our study the awareness level of general

Table 1: *Comparison of Study Variables Regarding Patients Visiting Public or Private Health Facility*

		Group		Total	p-value
		Private	Public		
Gender	Male	564(55.7%)	558(72.1%)	1122(62.8%)	<0.001*
	Female	449(44.3%)	216(27.9%)	665(37.2%)	
Dentist Visit	Never	398(39.3%)	419(54.1%)	817(45.7%)	<0.001*
	0-6	125(12.3%)	79(10.2%)	204(11.4%)	
	7-12	216(21.3%)	125(16.1%)	341(19.1%)	
	Once in 2 years	274(27.0%)	151(19.5%)	425(23.8%)	
Brushing Frequency	Once a day	602(59.4%)	402(51.9%)	1004(56.2%)	0.015*
	Twice a day	388(38.3%)	357(46.1%)	745(41.7%)	
	More than once a day	20(2.0%)	13(1.7%)	33(1.8%)	
	Occasionally	3(0.3%)	2(0.3%)	5(0.3%)	
Trauma	No sign of injury	946(93.4%)	753(97.4%)	1699(95.1%)	<0.001*
	Treated injury	13(1.3%)	6(0.8%)	19(1.1%)	
	Enamel fracture only	30(3.0%)	12(1.6%)	42(2.4%)	
	Enamel and dentine fracture	19(1.9%)	1(0.1%)	20(1.1%)	
	Pulpal involvement	4(0.4%)	0(0.0%)	4(0.2%)	
	Missing tooth due to trauma	0(0.0%)	1(0.1%)	1(0.1%)	
	Other damage	1(0.1%)	0(0.0%)	1(0.1%)	
Intervention Urgency	No treatment needed	130(12.8%)	80(10.3%)	210(11.8%)	<0.001*
	Preventive treatment needed	366(36.1%)	363(46.9%)	729(40.8%)	
	Prompt treatment including scaling	440(43.4%)	301(38.9%)	741(41.5%)	
	Immediate treatment needed	65(6.4%)	25(3.2%)	90(5.0%)	
	Referred for comprehensive evaluation	12(1.2%)	5(0.6%)	17(1.0%)	

population was below average. To keep oral hygiene good, proper brushing and cleaning aid like mouth wash and floss are required. These are simple but very effective things. There is a great need of improving oral hygiene of general public by awareness through workshops, seminars and television advertisement.[14]

In our study similar to previous studies brushing frequency was high. Most of the patients reported brushing their teeth twice a day. But the issue was inappropriate brushing pattern. Most of the patients brush in the circular pattern.[4,15] A recently study has reported an association between flossing and late decay of tooth.[16] Research revealed that use of cleaning aids like tooth pick, floss or mouthwash was very little.[3]

There are many factors contributing in dental health. A local study found that tooth loss is more frequent in diabetic patients than normal people.[17] In our study the frequency of decayed tooth was high but history of diabetes was not observed. It's been observed that the patients aged between 20 to 40 years were more prone to dental anomalies. Patients of this age group must be focused for oral hygiene awareness.[18] A previous study reveals that molar teeth were frequently extracted in our population aged below 40 years. The leading cause of these procedures was dental caries followed by periodontal diseases.[8,9] There are certain behavioral factors that have proportional effect on oral hygiene like alcohol or smoking habits that reverse the effect of brushing and mouthwash usage.[19] Hence it is determined from the study that there is immense need of awareness regarding oral hygiene and eating habits in our population.

CONCLUSIONS

In current study, awareness regarding oral health was lacking in majority of patients. The main reason is not considering the dental visits as preventive behavior. Dental visits depend mostly on patient's treatment need. There is a dire need to edu-

cate general public regarding proper dental care and prevention of major oral health problems through community outreach programmes and usage of mass media. It is suggested that oral health education should be incorporated into curriculum of students at an early stages of life.

Conflict of Interest

Authors declared no conflict of interest. This study was not funded by any organization or institute.

REFERENCES

1. Alaluusua S, Malmivirta R. Early plaque accumulation: a sign for caries risk in young children. Community Dent Oral Epidemiol. 1994; 22(5): 273-76.
2. Benzian H, Bergman M, Cohen L, Hobdell M, Mackay J. Advocacy for global oral health The UN High-level meeting on prevention and control of non-communicable. 2014.
3. Khan. ZA, Qureshi. B, Anwer. U, Asghar. Sk, Fatima. K. Frequency of Associated Factors Causing Dental Caries in patients Reporting at Tertiary Care Hospital. J Pak Dent Assoc. 2019;28(3):118-21.
4. Abideen Z, Tahir B, Hussain F. Knowledge, Attitudes and Practice regarding the Oral Health. Ophthalmol Update. 2018;16(4):885-9.
5. Desai K, Patel S. Assessment of oral hygiene awareness among college students in Surat City. Nat J Community Med. 2018;9:236-9.
6. Kanwal S, Hameed W. Frequency of Dental Caries in patients Undergoing Orthodontic Treatment. Pak J Med Health Sci. 2014;8(1):219-20.
7. Rafiq M, Hasan R, Bano M. Prevalence of dental caries and periodontal disease among elderly patients attending private dental college Karachi: a hospital based cross sectional study. Pak Oral Dental J. 2018;38(4):500-2.
8. Yasser F, Ghumman N, Atif S. Frequency and reasons for tooth extraction at institute of dentistry, CMH Lahore Medical College. Pak J Surg. 2016; 32(3):185-8.
9. Khan S, Ullah A, Ahmad W, Baig B, Sadiq M, Liaqat S. Frequency and pattern of removal of teeth in a sample of population of southern Punjab. Pak Oral Dental J. 2018;38(1):75-8.
10. Siddiqui T, Wali A, Azimi M, Salehi T, Siddiqui S. Socioeconomic Status and Dental Caries: Exploring the Relation in patients Visiting Dental Teaching Hospital, Karachi. J Pak Dent Assoc. 2019;28(1):27-32.
11. Chachar Z, Das G, Ahmed S, Khokhar M, Shaikh M, Mushtaque K. Periodontal disease in ideal weight, overweight and obese patients in different gender of a tertiary care hospital in pakistan. Professional Med J. 2019;26(09):1461-5.
12. Chaudhry S, Khan A, Butt A, Idrees M, Izhar M, Iqbal H. Helicobacter pylori in dental plaque; is it related to brushing frequency, plaque load and oral health status? J Coll Physicians Surg Pak. 2011; 21(10):589-92.
13. Recommendation P. STROBE Statement-Checklist of items that should be included in reports of. FilesFigshareCom [Internet]. (1):1–2. Available from: http://files.figshare.com/422353/ Checklist_S1.doc
14. Al Amassi BY, Al Dakheel RS. Oral hygiene practice of adult diabetic patients and their awareness about oral health problems related to diabetes. Journal of Dentistry and Oral Hygiene. 2017;9(2):8-14.
15. Manju J, Krithika C, Koteshwari P, Kumar GM. Awareness of Oral Hygiene Aids among General Population. Indian Journal of Forensic Medicine & Toxicology. 2020;14(3):411-5.
16. Go E-j. Oral Hygiene Management and Awareness of Calculus Removal in Some of the Elderly. Journal of Korean Dental Hygiene Science. 2020;3(1):1-13.
17. Kausar S, Burney S, Rehman K, Jahanzab Z, Zulfiqar A, Shoaib A. Frequency of Periodontitis in Diabetes patients. a Hospital Based Study. J Islamic Int Med Coll. 2019;14(3):150-5.
18. Khan A, Mariyum S, Shah S, Rehman S, Tirmazi S. Frequency and distribution of dental caries in teeth and arches of patients examined at Punjab dental hospital, Lahore. Pak Oral Dental J. 2015;35(4):687-90.
19. Friemel J, Foraita R, Günther K, Heibeck M, Günther F, Pflueger M, et al. Pretreatment oral hygiene habits and survival of head and neck squamous cell carcinoma (HNSCC) patients. BMC Oral Health. 2016;16(1):33.

COMPARISON OF PREMEDICATION WITH MIDAZOLAM VERSUS NORMAL SALINE (AS PLACEBO) PRIOR TO CAESAREAN SECTION IN OBSTETRICS PATIENTS FOR REDUCTION IN MATERNAL ANXIETY

Muhammad Imran Aslam,[1] Aamir Bashir,[2] Aamir Waseem[3]

How to cite: Aslam MI, Bashir A, Waseem A. Comparison of premedication with midazolam versus normal saline (as placebo) prior to caesarean section in obstetrics patients for reduction in maternal anxiety. JAIMC. 2021; 19(1): 118-123.

Abstract

Objective: To compare mean anxiety scores in obstetric patients undergoing caesarean section, which are pre-medicated with midazolam versus normal saline (as placebo). It was a randomized controlled trial, conducted in the Department of Anesthesiology, Shalamar Hospital, Lahore, from 15th September, 2017 to 14th March, 2018.

Methodology: A total of 100 patients of ages between 18 and 40 years indicated for caesarean section were included. Patients with hypertension, antepartum haemorrhage and congenital malformations and contraindicated for regional anaesthesia were excluded. The patients were randomized to receive either intravenous premedication with 0.025 mg/ kg midazolam (group M, n = 50) or an equal quantity of Normal Saline (group S, n = 50). The Amsterdam Preoperative Anxiety and Information Scale (APAIS) was used for the objective analysis of anxiety in all patients.

Results: The mean age of patients in group M was 28.38 ± 6.50 years and in group B was 27.84 ± 5.83 years. The mean weight of patients in group M was 63.44 ± 9.18 kg and in group S was 62.90 ± 9.16 kg. In this study, mean anxiety score was 8.92 ± 2.62 for midazolam group as compared to 17.38 ± 3.28 of saline group with a p value of 0.0001.

Conclusion: This study concluded that mean anxiety scores is less in obstetric patients, scheduled for elective caesarean section under regional anaesthesia technique, who were administered sedation using midazolam as compared to those receiving normal saline.

Key Words: caesarean section, midazolam, anxiety score.

Anxiety is a natural reaction arising in response to entering a different environment, such as an operating theatre. The role of sedation is important in such scenarios as the pregnant woman's anxiety and preoperative stress are intense.[1] While sedation has a wide sphere of use in today's regional anaesthesia procedures, its probable depressant effect on the new born in Caesarean section operation explains its rare or non-existent employment.

Midazolam is the benzodiazepine most commonly used for sedation, since it produces a faster onset , more complete amnesia, less pain on injection, and improved awakening when compared with diazepam. Midazolam possesses a relatively high volume of distribution (V_d) compared with other benzodiazepines because of its lipophilicity. The V_d is greatly amplified in obese patients, resulting in an increased half-life from 2.7 hours to 8.4 hours. Midazolam is cleared by hepatic hydroxylation to 1-hydroxymidazolam (elicits about 10% of the pharmacologic activity as parent compound). In comparison, diazepam has an extremely long half-life (0.8-2.25 d) that is markedly increased in obese

1. Muhammad Imran Aslam 2. Aamir Bashir
3. Aamir Waseem
1-3. Department of Anaesthesia, Shalamar Medical & Dental College, Lahore

Correspondence:
Dr. Muhammad Imran Aslam, Department of Anaesthesia, Shalamar Medical & Dental College, Lahore

Submission Date: 15-11-2020
1st Revision Date: 02-12-2020
Acceptance Date: 10-12-2020

or elderly patients (3.9 d and 3.29 d, respectively). Additionally, its active metabolites have long half-lives (i.e. N -desmethyldiazepam[1.6-4.2 d]; nordiazepam [about 8 d]).[2]

While there are several studies concerning the use of midazolam in regional anaesthesia, the number of studies regarding its use in Caesarean section is limited. Although it crosses the placental barrier, in small doses, it does not cause any adverse effects in the neonate.[2,3] The preoperative stress response leads to vasoconstriction in the uterine arteries and may cause fetal distress.[4] Many researchers have reported that increased preoperative anxiety means the use of more peri-operative as well as postoperative analgesia and longer hospitalization.[5]

In a study by Senel AC et al, patients undergoing caesarean section under regional anaesthesia, who received midazolam 0.025 mg/kg as premedication had significantly low anxiety scores (p = 0.0001) and the new born Apgar scores were not reported to differ between the group administered the midazolam and the control group (p>0.05).The baseline anxiety scores in both groups were comparable i.e. 18.24 ± 4.23 and 17.84 ± 3.77 with a p value of 0.725. However, anxiety scores were lower in the group after premedication with midazolam i.e. 10.84 ± 3.51 as compared to 15.00 ± 3.29 in the control group with a significant p value of 0.0001. Also the APGAR score at 5th minute after birth was 9.12 ± 0.58 and 9.16 ± 0.73 in both groups with a p value of 0.83.6

In another prospective randomized controlled trial, mothers pre-medicated with low doses of midazolam showed a lower level of preoperative anxiety and a higher degree of postoperative satisfaction than the control group. The preoperative anxiety scores of two groups before any premedication were 17.10±3.19 and 16.81±2.60 with a p value of 0.618. After premedication, anxiety score was11.98±1.99 for midazolam group as compared to 14.15±2.11 of control group with a p value of 0. The APGAR scores 5 minutes after birth were 9 in both groups. No significant differences were found between the two groups regarding the Apgar scores of the new born and the pH, $PaCO_2$, PaO_2, and base deficit in the umbilical arterial samples (p>0.05).[7]

This study was intended to compare anxiety scores in obstetric patients scheduled for elective Caesarean section under regional anaesthesia technique, in groups administered sedation using midazolam or without sedation. This will help us to improve our practice and will update local guidelines as well.

METHODOLOGY

After approval of hospital ethics committee, 100 patients were included in the study through operational theatre of obstetrics and gynaecology at Shalamar hospital, Lahore. After taking informed written consent from the participant cases, demographics were noted (name, age, weight). Patients of ages between 18 and 40 years scheduled for Caesarean section with ASA physical status I & II were included in the study. Patients with Systemic problems e.g.hypertension (BP>140/90mmhg), Diabetes mellitus (BSR>186mg/dL), obstetric complications such as antepartum haemorrhage and cases contraindicated for regional anesthesia or refusing a regional anaesthetic technique were excluded from the study. The patients were randomized to receive either intravenous premedication with 0.025 mg/ kg midazolam (group M, n = 50) or an equal quantity of Normal Saline (group S, n = 50) in the operating room before surgery by coin tossing method. All patients were booked on a morning list, instructed for the same preoperative fasting protocol and were educated as to how to complete the questionnaires required for the study. On arrival of the patients to the operation theatre, routine monitoring (electrocardiography, pulse oximetery, and a non-invasive blood pressure cuff) were applied, and venous access established for the infusion of lactated Ringer's solution.

After the institution of spinal anaesthesia, group (M) was given intravenous premedication with midazolam (0.025 mg/kg) in 2 mL solution, whereas

group (S) was given an equal quantity of normal saline. Same anaesthesia personnel administered the medication to either group. The Amsterdam Preoperative Anxiety and Information Scale (APAIS) was used for the objective analysis of anxiety in all patients. It consisted of six questions receiving a score between one (none) and five (most), with a total score of 30, investigating patient's concerns and anxiety. It is short, reliable, and easy to administer. APAIS was applied twice by the same anaesthesia assistant to all patients in the operating theatre before and after the completion of surgery. All spinal blocks were performed by the researcher himself. For spinal anaesthesia, 12 mg of intrathecal hyperbaric bupivacaine (0.75%) was injected using a 25-gauge spinal needle with patients in the sitting position at the L 3/4 interspace, under strict aseptic precautions. Parturient were then immediately placed in the tilted supine position. The level of sensory block was determined with cold and pinprick tests. Oxygen by nasal cannula (2 L/min) was applied to all patients. Urinary catheterization was performed, and surgery was started when a sufficient level of sensory block (T4) is achieved. Following spinal anaesthesia, systolic arterial blood pressure was maintained above 90 mmHg. Cases falling below this level were given 10-50 ug intravenous boluses of phenylephrine. Anxiety scores was recorded just before and after the surgery (as per operational definition). After completion of surgery, patients were kept in the recovery room for 1 hour and then shifted to the ward when they fulfil criteria.

Data were entered and analysed into SPSS version 21. Quantitative variables such as age and weight were presented as mean and standard deviation. Both groups were compared for anxiety score by applying independent t test with p value ≤0.05 as significant. Data were stratified for age, weight to address effect modifiers. Post-stratification independent sample 't' test was applied with p-value ≤0.05 as significant.

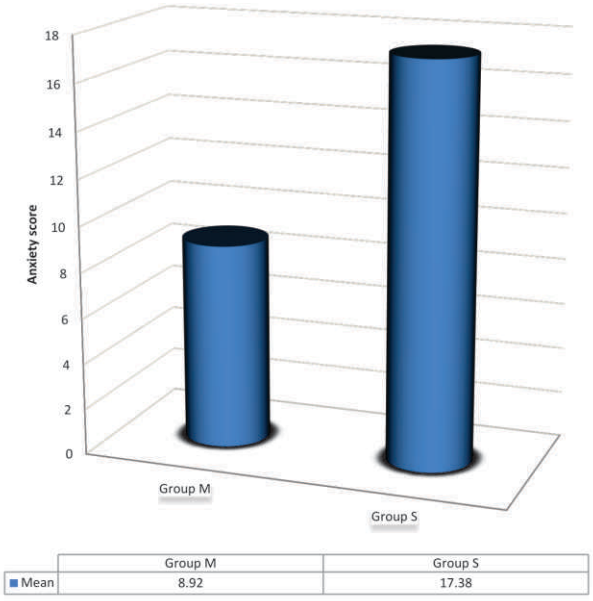
RESULTS

Age range in this study was from 18 to 40 years with mean age of 28.13 ± 6.12 years. The mean age of patients in group M was 28.38 ± 6.50 years and in group B was 27.84 ± 5.83 years. Majority of the patients 60 (60.0%) were between 18 to 20 years of age as shown in Table I. The mean weight of patients in group M was 63.44 ± 9.18 kg and in group S was 62.90 ± 9.16 kg (Table II).

The mean anxiety score was 8.92 ± 2.62 for midazolam group as compared to 17.38 ± 3.28 of saline group with a p value of 0.0001 as shown in Figure I.

Table 1: *Age Distribution for Both Groups (n=100)*

Age (years)	Group M (n=50)		Group S (n=50)		Total (n=100)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
18-30	28	56.0	32	64.0	60	60.0
31-40	22	44.0	18	36.0	40	40.0
Mean±SD	**28.38 ± 6.50**		**27.84 ± 5.83**		**28.13 ± 6.12**	



P-value = 0.0001 which is statistically significant

Figure I: *Mean Anxiety Scores in Obstetric Patients Undergoing Caesarean Section in both Groups*

DISCUSSION

Patients scheduled for surgery experience varying levels of anxiety, due to different factors like,

Table 2: *Weight for both groups (n=100).*

Weight (kg)	Group M (n=50)		Group S (n=50)		Total (n=100)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
⩽ 60	21	42.0	23	46.0	44	44.0
>60	29	58.0	27	54.0	56	56.0
Mean±SD	63.44 ± 9.18		62.90 ± 9.16		63.13 ± 9.17	

cultural diversity, type of surgery, previous anaesthesia experience, and preoperative information.[8,9] Previous studies have reported anxiety of being awake during surgery as one of the most common reasons for choosing general anaesthesia (GA),[10,11] but whether higher level of preoperative anxiety influences patient's decision to refuse regional anaesthesia (RA) needs to be determined. Literature has reported a higher level of preoperative anxiety in obstetric patients compared to general surgical population.[12,13] Caesarean section (CS) is one of the most common surgical procedures performed on obstetric patients, and regional anaesthesia is the preferred technique of anaesthesia in terms of risk and benefits for both mother and fetus. In modern obstetric anaesthesia practice, percentage use of regional anaesthesia for Caesarean section has become a marker of quality[14]. Like all surgical patients, obstetric patients also feel operative stress and anxiety. This can be prevented by giving patients detailed information about their operation and with preoperative pharmacological medications. Because of depressive effects of sedatives on new born, pharmacological medications are omitted, especially in obstetric patients. The literature contains few studies concerning preoperative midazolam use in caesarean section patients.[15]

I have conducted this study to compare mean anxiety scores in obstetric patients undergoing caesarean section, which were pre-medicated with midazolam versus normal saline (as placebo). Age range in this study was from 18 to 40 years with mean age of 28.13 ± 6.12 years. The mean age of patients in group M was 28.38 ± 6.50 years and in group B was 27.84 ± 5.83 years. Majority of the patients 60 (60.0%) were between 18 to 20 years of age. In this study, mean anxiety score was 8.92 ± 2.62 for midazolam group as compared to 17.38 ± 3.28 of saline group with a p value of 0.0001. In a study by Senel AC et al, patients undergoing caesarean section under regional anaesthesia, who received midazolam 0.025 mg/kg as premedication had significantly low anxiety scores (p=0.0001) and the new born Apgar scores were not reported to differ between the group administered the midazolam and the control group (p>0.05). The baseline anxiety scores in both groups were comparable i.e. 18.24 ± 4.23 and 17.84 ± 3.77 with a p value of 0.725. However, anxiety scores were lower in the group after premedication with midazolam i.e. 10.84 ± 3.51 as compared to 15.00 ± 3.29 in the control group with a significant p value of 0.0001.[6]

Premedication to facilitate neuraxial blockade remains the rare exception in pregnant patients, based on concerns about potential untoward effects of fetal drug exposure. In fact, in the 1960's several case reports described decreased motor tone in infants born to mothers who had been treated with diazepam during their pregnancy.[12] Another reason for the relative infrequent use of benzodiazepines during pregnancy is probably related to their putative association with facial malformations in animals when given during the teratogenic period of pregnancy, although, in a recent review, the alleged association of benzodiazepine use during pregnancy with facial malformations has been completely dismissed.[16,17] Therefore, women in some cases may endure a great deal of anxiety and discomfort when undergoing placement of a spinal or epidural block for Caesarean delivery.

In another prospective randomized controlled trial, mothers pre-medicated with low doses of midazolam showed a lower level of preoperative anxiety and a higher degree of postoperative satisfaction than the control group. The preoperative anxiety scores of two groups before any premedication were 17.10±3.19 and 16.81±2.60 with a p value of 0.618. After premedication, anxiety score was11.98±1.99

for midazolam group as compared to 14.15±2.11 of control group with a p value of 0. Sun GC et al., studied the effects of two diffe-rent doses of midazolam premedication on age and gender. In this study the dosage of intravenous mida-zolam chosen were 0.02 and 0.06 mg/kg midazolam. They concluded that midazolam is effective for producing sedation and anxiolytic effect at a dose of 0.02 mg/kg, with minimal effects on cardio-respira-tory system and oxygen saturation to patients.[18] In a placebo controlled trial comparing the effects of 0.025 mg/kg midazolam with saline in patients undergoing caesarean section, it was found that anxiety scores were lower in mothers receiving intravenous midazolam. These findings were similar to our findings where midazolam premedication considerably reduced the anxiety scores.[19]

CONCLUSION

We concluded that mean anxiety score is less in obstetric patients, scheduled for elective cesarean section under regional anesthesia technique, who are administered sedation using midazolam as compared to those receiving normal saline. So, we recommend that premedication with midazolam in patients undergoing cesarean section should be used routinely in our general practice for preventing anxiety.

Ethical Approval

Ethical approval was obtained from the Hospital Review Committee.

Patients' Consent

Informed consent was signed by every patient before enrolment in the study.

Conflict of Interest

Authors declared no conflict of interest.

Authors' Contribution

Muhammad Imran Aslam: Conceived idea, study designed, Data Collection.

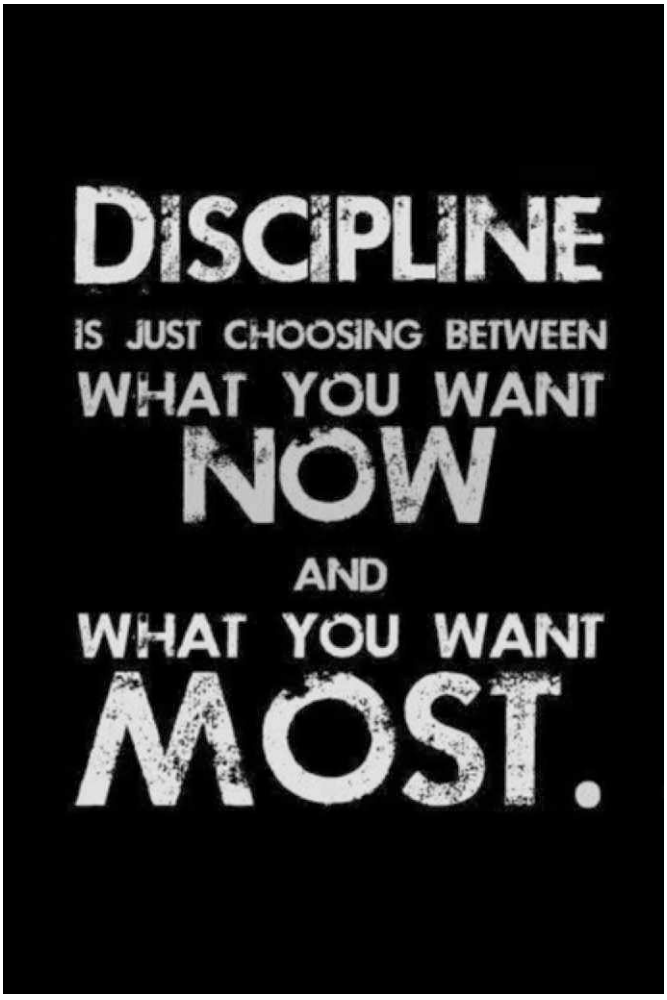
Aamir Bashir: Data collection, literature review, Manuscript writing

Aamir Waseem: Data Analysis, Manuscript writing, Proof reading

REFERENCES

1. Maheshwari D, Ismail S. Preoperative anxiety in patients selecting either general or regional anesthesia for elective cesarean section. J Anaesth Clin Pharmacol 2015; 31:196-200
2. Mattingly JE, D'Alessio J, Ramanathan J. Effects of obstetric analgesics and anesthetics on the neonate: A review. Paediatr Drugs. 2003;5:615–27.
3. Han G, Li L. Tian Y, Xue H, Zhao P. Influences of Different Doses of Midazolam on Mother and Fetus in Fetoscopic Surgery for Twin-to-Twin Transfusion Syndrome. Pharmacol 2015;96:151-154.
4. Aksoy AN, Aydin F, Kucur SK, Gözükara I. Maternal and fetal Doppler velocimetry in women diagnosed with fear of childbirth. Niger J Clin Pract 2016; 19:632-5.
5. Robleda G, Sillero-Sillero A, Puig T, Gich I, Baños J-E. Influence of preoperative emotional state on postoperative pain following orthopedic and trauma surgery. Rev. Latino-Am. Enfermagem. 2014; 22: 785-791.
6. Senel AC, Mergan F. Premedication with midazolam prior to caesarean section has no neonatal adverse effects. Braz J Anesth. 2014;64:16–21.
7. Mokhtar AM, Elsakka AI, Ali HM. Premedication with midazolam prior to cesarean delivery in preeclamptic parturients: A randomized controlled trial. Anesth, Essays and Researches. 2016;10(3):631-636.
8. Carvalho B, Cohen SE, Lipman SS, Fuller A, Mathusamy AD, Macario A. Patient preferences for anesthesia outcomes associated with cesarean delivery. Anesth Analg 2005;101:1182-7.
9. Jawaid M, Mushtaq A, Mukhtar S, Khan Z. Preoperative anxiety before elective surgery. Neurosciences (Riyadh) 2007;12:145-8.
10. Shevde K, Panagopoulos G. A survey of 800 patients' knowledge, attitudes, and concerns regarding anesthesia. Anesth Analg 1991;73:190-8.
11. Kennedy BW, Thorp JM, Fitch W, Millar K. The theatre environment and the awake patient. J Obstet Gynaecol 1992;12:407-11.
12. Jafar MF, Khan FA. Frequency of preoperative anxiety in Pakistani surgical patients. J Pak Med Assoc 2009;59:359-63.
13. Beilin Y, Rosenblatt MA, Bodian CA, Lagmay-Aroesty MM, Bernstein HH. Information and concerns about obstetric anesthesia: A survey of 320 obstetric patients. Int J Obstet Anesth 1996;5:145-51.

14. Maheshwari D, Ismail S. Preoperative anxiety in patients selecting either general or regional anesthesia for elective cesarean section. J Anaesthesiol Clin Pharmacol 2015;31:196-200.
15. Haram K. "Floppy infant syndrome" and maternal diazepam (Letter). Lancet 1977; 2: 612–3.
16. Dolovich LR, Addis A, Vaillancourt JM, Power JD, Koren G, Einarson TR. Benzodiazepine use in pregnancy and major malformations or oral cleft: metaanalysis of cohort and case-control studies. BMJ 1998;317: 839–43.
17. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med 1998; 338: 1128–37.
18. Sun GC, Hsu MC, Chia YY. Effects of age and gender on intravenous midazolam premedication: a randomized double-blinded study. BJA. 2008; 101: 632-39.
19. Ahmet C, Fatih M. Premedication with midazolam prior to caesarean section has no neonatal adverse effects. 2014;64:16-21.



PERCEPTIONS AND PRACTICES OF MEDICAL STUDENTS TOWARDS SHISHA SMOKING

M. Ahmad Mustansir,[1] Mahnoor Azhar,[2] Iram Zahra,[3] M. Ahsan Ajmal,[4] Khadija Zahid[5]

How to cite: Mustansir MA, Azhar M, Zahra I, Ajmal MA, Zahid K. Perceptions and practices of medical students towards shisha smoking. JAIMC. 2021; 19(1): 124-128.

Abstract

Background : Shisha Smoking has become increasingly popular among the urban youth population. 22.7% medical students smoke shisha with the number increasing at an alarming rate. Understanding perceptions and factors behind the rise in the prevalence of shisha smoking is important for the development of prevention strategies and policies.

Objective: To assess the perception and practices of shisha smoking among medical students. Subjects and Methods:

Methodology: It was a cross sectional study conducted from February to May 2019 at Allama Iqbal Medical College, Lahore. 307 medical students fulfilling the inclusion criteria were included in our study. All students voluntarily opted to fill the questionnaire. Every student was given a structured questionnaire, strategically divided into parts pertaining to knowledge, attitude and practices linked to shisha smoking. Data was entered and analyzed in SPSS v25.0. Mean and SD were calculated for numerical variables such as age. Frequency and percentages were calculated for nominal variables like gender, cigarette smoking status, perception and practices.

Results: 50.2% were males and 49.8% were females. Mean agewas 20.9 +0.898 years. 97.0% males and 94.0% females had heard about Shisha smoking with 80.5% males getting information from friends, and 13.0% from social media as compared to females whereby 51.0% got information about Shisha from friends and 37.3% from social Media, the differences being statistically significant on a Chi Square Test ($p<0.05$). 16.2% of the male shisha smokers started smoking out of curiosity, 6.5% due to peer pressure, and 4.5% due to anxiety/stress. For females, 6.5% started due to curiosity, 2.0% due to peer pressure, and 2.0% due to anxiety/stress. ($p<0.05$).

Conclusion: The rates and prevalence of Shisha smoking in medical students is considerably high. Males have significantly higher rates of shisha smoking as compared to female medical students.

Keywords: Perception, shisha, smoking, medical students

Shisha is becoming an increasingly popular method of tobacco use worldwide. Originating in India in the 15th century, shisha smoking spread to the Eastern Mediterranean region, the trend setting in the Ottoman Empire and Egypt by the 16th century. Initially being prevalent in the male gender, in the 19th century, the practice of shisha smoking also started spreading amongst women in the Middle East.

Now, its use has gradually increased in Europe and USA. Known by different names such as 'hubble-bubble', 'hookah', 'goza', or 'narghile' in different cultures, shisha or the water-pipe has become a fashion and is used in social settings like cafes and restaurants, in addition to being used by urban youth, young professionals, college and university stu-dents.[2,3] It has also been reported that shisha smoking is prevalent in medical colleges of Pakistan.

1. M. Ahmad Mustansir
2. Mahnoor Azhar
3. Iram Zahra
4. M. Ahsan Ajmal
5. Khadija Zahid

1-5. Department of Community Medicine, Allama Iqbal Medical College, Lahore.

Correspondence:
Dr. M. Ahmad Mustansir, Allama Iqbal Medical College, Lahore
E-mail: ahmadbutt250@gmail.com

Submission Date: 09-11-2020
1st Revision Date: 21-11-2020
Acceptance Date: 28-11-2020

Although multiple health hazards have been linked to shisha smoking, the population at large has not yet fully understood the associated risks, and therefore a common misconception prevails in the society that water-pipe is relatively less hazardous than smoking tobacco cigarettes.[2] This erroneous perception is also prevalent in the Pakistani society, mainly due to the purported filtering effect of water through which the smoke passes before it is inhaled.[4] Shisha has now emerged as a global public health concern and has been described as the 'emerging deadly trend'. Water-pipe smoking has been significantly linked with similar diseases attributable to cigarette smoking and even more. It is projected that the attributable mortality due to tobacco smoking will increase from 3 million deaths in 1990 to 8.[4] million deaths in 2020.[5] The aerosol of shisha smoke is reported to contain high concentrations of carbon monoxide, nicotine, tar, and heavy metals at concentrations which are as high as or even higher than those among the cigarette smokers and which are highly toxic to the human body.[5] Furthermore, the practice of water-pipe smoking is also a source of spreading infections such as tuberculosis, mononucleosis, viruses and bacteria when the mouth piece is shared. Other factors which drastically increase its association with pulmonary, gastrointestinal, cardiovascular and hematological disorders include the fact that it is smoked over coal which has a cumulative effect on the already present toxins and that a shisha smoker inhales up to 200 times more smoke in a single session as compared to cigarette smokers.[6] In the USA, this behavior has been rapidly growing, especially among young college students.

Convenience sample surveys have suggested 30-day college water-pipe tobacco smoking rates as high as 15-20% and a college based random sample survey found a 30-day use rate of 9.5%, a one-year use rate of 30.6% and an ever use rate of 40.5%.[7] With this being said, none of the few studies conducted in Pakistan on smoking habits has explicitly discussed the behavioral aspects, knowledge and attitudes of medical students towards shisha smoking.

Our research will, therefore, offer a new, much awaited insight into the perceptions and practices of medical students towards shisha smoking, supported by accurate and relevant statistical data

METHODOLOGY

Three hundred and seven medical students fulfilling the inclusion criteria were included in the study. After informed consent and approval from ethical community of Allama Iqbal Medical College a detailed demogra-phic information was collected and each student was given a structured questionnaire strategically divi-ded in parts to collect relevant information. Data was entered and analyzed in SPSS version 25. Mean and Standard Deviation were calculated Mean and SD were calculated for numerical variables such as Subject Age and year of study. Frequency and per-centages were calculated for nominal variables like Gender and Cigarette Smoking Status of the Subject. Cross Tabulation was done for Shisha smoking status of the subject and his/her siblings and parents.

RESULTS

A total of 307 medical students of Allama Iqbal Medical College were taken from all classes, who fulfilled our inclusion criteria. All the students were willing and cooperative for partici-pation in research. Of these 307 students, 50.2% were male and 49.8% were female. The mean age of participants was 20.92 with a standard deviation of 1.898, with 88.9% of the participants falling below the age of 23 years. Of the participants, 20.2% were from 1st year, 19.9% from 2nd Year, 19.5% from 3rd Year, 20.8% from 4th Year, and 19.5% from Final Year. Out of the total participants, 45.9% had the residential status of a Day scholar, while 54.1% lived as hostelites. (Table 1).95.1% of the participants were found to have prior knowledge of Shisha Smoking/Hubble Bubble, with 65.8% getting the knowledge from friends and 25.1% from social media. A surprising 38.1% subjects consider it less

hazardous than cigarette smoking and 22.8% believe that Shisha smoking is culturally acceptable. The cross tabulation analysis showed that the difference in the source of information between male and female subjects is statistically significant with an X^2 value (0.000). A similar result from the cross tabulation analysis shows that the difference in the response upon insistence is significant between the two genders of the study subjects X^2 value (0.007)

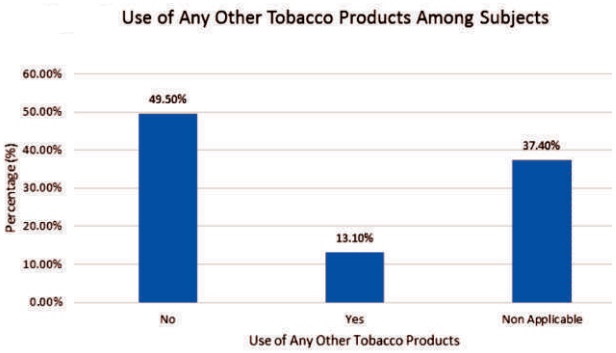
The analysis of questionnaires for practices of study subjects about Shisha Smoking, 21.8% of the subjects had smoked Shisha at least once. An astonishing 47.4% of the study subjects had at least one friend who smoked Shisha. 13.1% of the subjects used tobacco products other than Shisha. The cross tabulation analysis showed that the difference in starting age of Shisha smoking is statistically significant between male and female subjects X^2 value (0.000). Further cross tabulation analysis revealed that the difference in use of other tobacco products is statistically significant between male and female subjects with an X^2 value (0.001).

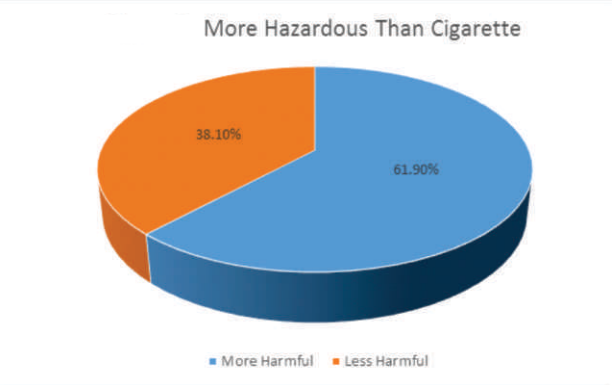
Table 1: Demographic Profile of Subjects

Variables n=	Frequency	Percent
Age Mean=20.92 SD1=.898 Min= 19 Max= 30		
< 23 years	273	88.9
> 23 years	34	11.1
Gender		
Male	154	50.2
Female	153	49.8
Year of Study		
First Year	62	20.2
Second Year	61	19.9
Third Year	60	19.5
Fourth Year	64	20.8
Final Year	60	19.5
Father Education		
Primary	43	14.0
Secondary	38	12.4
Tertiary	226	73.6
Mother Education		
Primary	53	17.3
Secondary	70	22.8
Tertiary	184	59.9

DISCUSSION

The main purpose of the study was to find out the prevalence, perception and practices of Shisha





Smoking among the medical students. As per our study, marked variation in perception and practices regarding Shisha Smoking was observed by gender. Our findings of male predominance in Shisha smoking rates correspond to previous similar studies, with our study finding that 31.8% of Shisha smokers were males and 11.8% were females.[4,9] This may be due to the cultural taboo associated with female Shisha smoking.

About 18.8% of the respondents were of the age group 17-20, this finding is in consistence with a similar study conducted among medical and dental students in Karachi, which found 32.8% of respondents to be of 17-18 years of age.[4] In our study, we found that the most common reason for the initiation of Shisha Smoking was curiosity (11.4%), followed by peer pressure (4.2%), anxiety/stress (3.3%) and others (4.6%). These findings are in line with similar studies.[2,5,8,10]

Our study found out that the major source of information about Shisha Smoking in study subjects

is friends (65.8%) followed by social media (25.1%) and print media (2.3%). The female participants were found to have gained more information from social media while the male participants were found to have gained more information from friends. This can be explained by the fact that Shisha Smoking is more prevalent in males as indicated by.[4,9] Overall, 22.1% of the respondents were open to Shisha Smoking upon insistence by friends and family, with males being more open (28.6%) as compared to females (15.7%), and the differences being statistically significant with X^2 value (0.007).

A study in Kigali, Rwanda found that 43.1% of the subjects had Shisha Smoker friend(s).[5,11] This value is comparable to the value obtained in our study, which is 47.4%. Our study found out that significantly more males (69.5%) had friends who were Shisha Smokers relative to females (24.7%) with differences achieving statistical significance with X^2 value (0.000). This can be explained in part to the overall high prevalence of Shish smoking in adult males and the habit of group Shisha Smoking in males. This is again related to the cafes and restaurants offering Shisha to the youth, which again signifies the increasing trend and hence the cultural acceptance of Shisha Smoking in the society especially the young adult age group.

As per our study, 13.1% of the respondents used other tobacco products, in addition to Shisha Smoking. This is supported by another study conducted in Karachi, Pakistan.[4] Males (20.1%) were more likely to use other tobacco products as compared to females (6.0%) with the difference achieving statistical significance with X^2 value (0.001). The high rates of tobacco smoking in addition to Shisha Smoking can be traced back to the cheap and easy availability to tobacco in Pakistan. Males report higher tobacco usage rates because of social acceptability and trend.

A study found out that 38.1% of the participants believed that Shisha Smoking is less harmful than cigarette smoking. This result is in congruence with a study conducted in Syria which found out that 30.0% of the participants were of a similar view.[13] This perception rests on the fact that the majority believes that Shisha Smoking is not harmful as the smoke gets filtered in the water mechanism.[1,4]

In response to the question of quitting Shisha Smoking in the future, 16.9% of the participants were found out to have no intention of doing so. Among these participants, the male population was almost double (22.7%) relative to the female population (11.1%). This trend is not surprising and may be due to group Shisha Smoking in males and the general acceptance of Shisha Smoking in the male population. Shisha contains nicotine and other chemicals which make it addictive, and hence the longer you smoke the less likely you are to quit.[3] This is also proven by our study which clearly indicates that around 70% of the respondents believe that Shisha Smoking is addictive.

Around 20% of the study subjects had thought of starting Shisha Smoking in the future, with 27.3% of them being males and 11.9% being females, which again is statistically significant with X^2 value (0.001). This can be explained by the fact that there is more acceptance of Shisha Smoking in male population, but also highlights the fact that an increasing trend is seen in the female population, as shown by a study in Kuwait.[12]

Acknowledgements

We are indebted to the assistance of our facilitator, Dr. Tahir Ismail for his continuous instruction and explanations. We cannot overlook the technical assistance provided by Dr. Mamoon Akbar; Thankyou sir for your support. We would extend our regards to Dr. Sana Iftikhar for proofreading the manuscript and providing valuable suggestions throughout the process.

Limitations of Study

1. The short questionnaire prevented in depth exploration of attitudes and behaviors about Shisha Smoking.
2. Because the data was self-reported, so recall bias and response bias may have tampered the

results.

3. The findings of the study were based in Allama Iqbal Medical College only and therefore may not represent the perceptions and practices of Shisha Smoking among medical students in general.

CONCLUSION

The trend of Shisha Smoking is increasing at an alarming rate with male medical students more prone to smoke, pick up Shisha Smoking and less likely to quit as compared to female smokers.

Curiosity seems to be the most important factor compelling the students to initiate Shisha Smoking which is in line with the trend seen in general population. Shisha Smoking seems to be an upgraded, trendy variant of tobacco smoking since a significant percentage of Shisha Smokers also use other tobacco products. This signifies that the widespread prevalence of Shisha Smoking is part of a general trend of tobacco smoking in Pakistan. Shisha Smoking practices seem to be influenced by peer pressure and group trends, since most smokers report having friends who also smoke.

Recommendations

The aforementioned conclusions warrant increased on campus Shisha surveillance, awareness drives to discourage the use of Shisha Smoking. A comprehensive anti-smoking policy for medical colleges and medical students is required for a long term solution to be achieved. Furthermore, additional research into Shisha Smoking paradigms is necessary to address the issue.

Conflicts of Interest: None

Funding Sources: None

REFERENCES

1. Aljarrah K, Ababneh ZQ, Al-Delaimy WK. Perceptions of hookah smoking: harmfulness: Predictors and Characteristics among current hookah users. Tobacco Induced Diseases Journal 2009; 5(16): 1-7 doi: 10.1186/1617-9625-5-16
2. Kumar A, Mahmud M, Hussain N, Abdul Nabi Z, Shah B, Rizvi N. Knowledge and Behavior of Physicians and Surgeons regarding Shisha Smoking. British Journal of Medicine and Medical Research 2016; 13(11): 1-12 doi: 10.9734/BJMMR/2016/24258
3. Wong LP, Alias H, Agha Muhammadi N, Agha Zadeh S, CheeWai Hoe V. Shisha Smoking Practices, Use Reasons, Attitudes, Health Effects and Intentions to Quit among Shisha Smokers in Malaysia. Int J Environ Res Public Health 2016; 13(7): 1-17 doi: 10.3390/ijerph13070726
4. Khan N, Siddiqui MU, Padhiar AA, Hashmi SA, Fatima S, Muzaffar S. Prevalence, Knowledge, Attitude and Practice of Shisha Smoking among Medical and Dental Students of Karachi, Pakistan. JDUHS 2008; 2(1): 3-10
5. Omotehinwa OJ, Japheths O, Damascene IJ, Habtu M. Shisha Use among Students in Private University in Kigali City, Rwanda: Prevalence and associated factors. BMC Public Health 2018; 18(713): 2-10 doi: 10.1186/s12889-018-5596-1
6. Sameer-ur-Rehman, Sadiq MA, Parekh MA, Zubairi AS, Frossard PM, Khan JA. Cross Sectional Study Identifying forms of Tobacco Use by Shisha Smokers in Pakistan, JPMA 2012; 62(2): 192-195
7. Primack BA, Walsh M, Bryce C, Eissenberg T. Water-Pipe Tobacco smoking among middle and high school students in Arizona. Pediatrics Journal 2009;123(2):282-288 doi:10.1542/peds.2008-1663
8. Al Zabadi H, Musmar H, Hassouna A, Shtaiwi D. Cigarettes and water pipe smoking prevalence, knowledge and attitudes among the Palestinian physicians in the West Bank. Tobacco Use Insights 2018; 11: 1-11 doi: 10.1177/1179173X18813369
9. Balogh E, Faubl N, Riemenschneider H, Balazs P, Bergmann A, Cseh K et al. Cigarette, Water pipe and e-cigarette use among an International sample of Medical Students. Cross Sectional Multicenter Study in Germany and Hungary. BMC Public Health 2018; 18(591): 2-10 doi: 10.1186/s12889-018-5494-6
10. Jawaid A, Zafar AM, Rehman TU, Nazir MR, Ghafoor ZA, Afzal O, et al. Knowledge, Attitude and Practice of University Students regarding water-pipe smoking in Pakistan. INT J Tuberc Lung Dis. 2008; 12(9): 1077-84
11. Zavery A, Qureshi F, Riaz A, Pervez F, Iqbal N, Khan JA. Water pipe (Shisha) use and legislation awareness against Shisha smoking among medical students: A study from Karach, Pakistan. J Community Health 2017; 42(3): 461-5
12. Mohammed H, Newman I, Tayeh R. Sheesha Smoking among a sample of Future teachers in Kuwait. Med MJ 2006; 38(2): 107-13
13. Almerie MQ, Matar HE, Salam N, Morad A, Abdulaal M, Koudsi A, et al. Cigarettes and Waterpipe smoking among Medical Students in Syria: a cross sectional study. Int J Tuberc Lung Dis 2008; 12: 1085-91

COMPARISON OF CONTINUOUS VERSUS INTERMITTENT PHOTOTHERAPY FOR MANAGEMENT OF NEONATES PRESENTING WITH NEONTAL HYPERBILIRUBINEMIA

Nayab Butt,[1] Rani Saba Urooj,[2] Sonia Zofishan,[3] Fozuia Ishaq,[4] Zenab Aziz,[5] Amna Sarwar[6]

How to cite: Butt N, Urooj RS, Zofishan S, Ishaq F, Aziz Z, Sarwar A. Comparison of continuous versus intermittent phototherapy for management of neonates presenting with neonatal htperbilirubinemia. JAIMC. 2021; 19(1): 129-132.

Abstract

Background: When skin is exposed to light, it hastens the excretion of bilirubin, the rate of photolysis is accelerated. On this note, continuous phototherapy should be more productive and proficient than the intermittent one. Nevertheless, efficacy of phototherapy is dependent upon the preliminary initial concentration of bilirubin. Henceforth, as the bilirubin concentration decreases the efficiency drops. Continuous phototherapy should be more effective than intermittent one.

Objectives: To compare the mean reduction in bilirubin level with continuous versus intermittent phototherapy for management of neonates presenting with neonatal hyperbilirubinemia.

Methodology: Randomized Controlled Trial was carried out at the Department of Paediatrics, Sir Ganga Ram Hospital SGRH, Lahore for six months 23-08-2017 to 22-02-2018. 100 neonates fulfilling selection criteria were enrolled. Those 100 neonates were divided in a random method into groups of two by applying lottery method. In Group A, continuous phototherapy was done for two hours and then half an hour off. In group B, intermittent phototherapy was done for one hour and then one hour off intermittently. Phototherapy was applied for 48 hours as scheduled for each group. Phototherapy units were identical in both methods. At baseline and after 48 hours 3cc blood samples were drawn in a syringe and sent to the hospital laboratory. Bilirubin level was noted.

Results: Mean reduction in bilirubin level in Group-A with continuous phototherapy is 7.22+0.97 and in Group-B with intermittent phototherapy is 8.42+0.73 (mg/dl), p value was 0.0001.

Conclusion: Mean reduction in bilirubin level with intermittent phototherapy was significantly higher.

Key Words: Neonatal hyperbilirubinemia, management, phototherapy, intermittent, continuous, mean reduction of bilirubin

Neonatal hyperbilirubinemia is very prevalent. Newborns mostly develop an unconjugated serum bilirubin level of >30µmol/L during the first seven days of life i.e., the first week of life.[1] It affects 60% of term and 80% of preterm infants.[2-3] Photo-therapy is the main stay of treatment of neonatal jaundice.[3] It is the primary treatment in neonates with unconjugated hyperbilirubinemia. This thera-peutic principle was discovered rather adventi-tiously, coincidentally and fortuitously in England in the 1950s and is now arguably the most common, feasible, widely accepted method of therapy of any kind used in newborns.[5]

One randomized trial showed that the mean reduction was 7.67+0.5mg/dl with continuous pho-totherapy and 7.03+0.03mg/dl with intermittent

1. Nayab Butt
2. Rani Saba Urooj
3. Sonia Zofishan
3. Sonia Zofishan
4. Fozuia Ishaq
5. Zenab Aziz
6. Amna Sarwar

1. *Azra Naheed Medical College/Ch.Mohammad Akram Teaching & Research Hospital, Lahore*
2. *Central Park Medical College, Lahore*
3. *Department of Paediatrics, Jinnah Hospital, Lahore/Allama Iqbal Medical College, Lahore.*
4. *Paediatrics Department, Sir Ganga Ram Hospital, Fatima Jinnah Medical University, Lahore*
5. *Paediatrics Department, Jinnah Hospital, Lahore.*
6. *Women Medical Officer, DHQ, Nankana Sahib*

Correspondence:
Dr. Nayab Butt, *Azra Naheed Medical College/Ch.Mohammad Akram Teaching & Research Hospital, Lahore,*
Email: nayab.butt1990@gmail.com

Submission Date: 21-11-2020
1st Revision Date: 18-12-2020
Acceptance Date: 22-12-2020

phototherapy for management of neonatal hyperbilirubinemia. The difference was found to be significant (P<0.05).[6] Another randomized trial showed that the mean reduction was 8.92+0.08mg/dl with continuous phototherapy and 9.26+0.06mg/dl with intermittent phototherapy for management of neonatal hyperbilirubinemia. The difference was found to be significant (P<0.05).[7]

But one randomized trial showed that the mean reduction was 4.7822+1.20231mg/dl with continuous phototherapy and 4.6341+1.18694mg/dl with intermittent phototherapy for management of neonatal hyperbilirubinemia. The difference was found to be insignificant (P>0.05).[8]

Rationale of this study was to compare the mean reduction in bilirubin level with continuous versus intermittent Phototherapy for management of neonates presenting with neonatal hyperbilirubinemia. We want to conduct this study to confirm which mode of phototherapy is more effective for treating neonatal jaundice, so that we can implement it in local population in future

METHODOLOGY

A randomized-control trial study was carried out at the Department of Pediatric Medicine, Sir Ganga Ram Hospital, Lahore for six months 23-08-2017 to 22-02-2018 using non-probability, consecutive sampling technique. Sample size of 100 neonates; each group comprised of 50 nenonate calculated with 95% confidence level, 80% power of study and taking magnitude of mean reduction in bilirubin level i.e. 7.67+0.5mg/dl with continuous phototherapy and 7.03+0.03mg/dl with intermittent phototherapy for management of neonatal hyperbilirubinemia.[6]

Term neonates with gestational age between 37 and 42 weeks, (by dating scan) weighing more than 2500g of 24-72 hours of age either gender presenting with neonatal hyperbilirubinemia bilirubin level >15mg/dl within 72 hours after birth were included.

Neonates on intensive care, congenital malformation like cardiac, skeletal, renal, syndromes and sepsis (positive blood culture), fits, reluctance to feed, platelets <5000,ABO incompatibility (mothers have O blood group and babies have A, B or AB) Rh incompatibility, Glucose 6 phosphate dehydrogenase deficiency (by direct measurement enzyme activity less than 10% of the normal), infants of diabetic mother (gestational diabetes at 24 to 26 weeks of gestation and Three-Hour Oral Glucose Tolerance shows glucose levels more than 165mg per dL at 2 hour and 145mg per dL at 3 hour), neonates having history of asphyxia (Apgar score <3 at 5 minutes), neonates born to mothers with any disease of bone, kidney (creatinine >1.3mg/dl) and liver (AST/ ALT >40IU/L) were excluded.

100 neonates fulfilling selection criteria were enrolled from emergency Department of Pediatrics, Sir Ganga Ram Hospital SGRH, Lahore. Informed consent was obtained from their parents. Demographic variables (name, gestational age at birth, gender, birth weight) were also noted down. Then neonates were divided in a random method into groups of two groups by applying the lottery method. Continuous phototherapy means 2 hours on and half an hour off. Intermittent phototherapy means one hour on and one hour off. In Group A, continuous phototherapy was done for two hours and then half an hour off. In group B, intermittent phototherapy was done for one hour and then one hour off intermittently. Phototherapy was applied for 48 hours as scheduled for each group. Phototherapy was given with LED kept 30 cm above the infants. An average irradiance of 20µW/cm^2/nm at 425 to 475nm is generated. Phototherapy units were identical in both methods. At baseline and after 48 hours 3cc blood samples were drawn in a syringe and sent to the hospital laboratory. Bilirubin levels were noted. Post-treatment serum bilirubin level was subtracted from baseline serum bilirubin level in terms of mg/dl to calculate the reduction in bilirubin. Treatment was given for 48 hrs. The reduction in bilirubin level was calculated. The information which was obtained was all noted down in a proforma.

The information and details regarding the cases

which was noted down in the proforma was typed in and analyzed on SPSS version 20. The quantitative variables which include age, birth weight, bilirubin level at baseline, bilirubin level after treatment and reduction in bilirubin level were shown as mean & standard deviation. Qualitative variables which here imply gender and gestational age (term/preterm) were shown as frequencies and percentages. Comparison of both the groups was done by using independent sample t-test for reduction in bilirubin level. P<0.05 was taken as significant Stratification of data was done for age, gestational age (<39 weeks, >39 weeks), gender and birth weight and bilirubin level at baseline. Comparsion of the stratified groups was done by using independent t-test. P <0.05 was taken as significant.

RESULTS

A total of 100 cases (50 in each group) fulfilling the inclusion/exclusion criteria were enrolled to compare the mean reduction in bilirubin level with continuous versus intermittent Phototherapy. Age distribution of the patients was done, it shows that 60% (n=30) in Group-A and 54%(n=27) in Group-B were between 24-48 hrs and 40%(n=20) in Group-A and 46%(n=23) in Group-B were between 49-72 hrs of life, mean+sd was calculated as 46.24+12.50 hrs in Group-A and 47.00+13.22 hrs in Group-B. Mean gestational age in Group-A and Group-B was 38.82+ 1.17 weeks and 39.00+1.25 weeks respectively. Gender distribution shows that 48%(n=24) in Group -A and 40%(n=20) in Group-B were male whereas 52%(n=26) in Group-A and 60%(n=30) in Group-B were females. Mean birth weight (grams) in Group-A was 2942+205.128 grams and 3008+229.320 grams in Group-B. Mean bilirubin levels (mg/dl) in Group-A was 17.62+0.94 (mg/dl) and 17.72+0.86 (mg/dl) in Group-B.

The data was stratified for age, gestational age (<39 weeks, >39 weeks), gender, birth weight and bilirubin level at baseline. Comparison of the stratified groups was made were by using independent t-test. P <0.05 was taken as significant.

DISCUSSION

When skin is exposed to light it hastens the excretion of bilirubin, so continuous phototherapy should show more promising results than the intermittent one. This study was to compare the mean reduction in bilirubin level with continuous versus intermittent Phototherapy for management of neonates presenting with neonatal hyperbilirubinemia. In this study, out of 100 cases (50 in each group), 60% (n=30) in Group-A and 54%(n=27) in Group-B were between 24-48 hrs and 40%(n=20) in Group-A and 46%(n=23) in Group-B were between 49-72 hrs of lie, mean+sd was calculated as 46.24+12.50 hrs in Group-A and 47.00+13.22 hrs in Group-B, comparison of mean reduction in bilirubin level with continuous versus intermittent phototherapy, it shows that in Group-A 7.22+0.97 and in Group-B 8.42+0.73 (mg/dl), p value was 0.0001.

We compared our results with a randomized trial

Table 1: *Comparison Of Mean Reduction in Bilirubin Level with Continuous Versus Intermittent Phototherapy for Management of Neonates Presenting with Neonatal Hyperbilirubinemia (n=100)*

Reduction of bilirubin levels (mg/dl) after treatment	Group-A (n=50)		Group-B (n=50)	
	Mean	SD	Mean	SD
	7.22	0.97	8.42	0.73

Table 2: *Stratification for Comparison of Mean Reduction in Bilirubin Level with Continuous Versus Intermittent Phototherapy for Management of Neonates Presenting with Neonatal Hyperbilirubinemia with Regards to Bilirubin Levels at Baseline (n=100).*

15-17mg/dl

Reduction of bilirubin levels (mg/dl) after treatment	Group-A (n=50)		Group-B (n=50)	
	Mean	SD	Mean	SD
	7.24	0.94	8.39	0.73

P value = 0.0001

15-17mg/dl

Reduction of bilirubin levels (mg/dl) after treatment	Group-A (n=50)		Group-B (n=50)	
	Mean	SD	Mean	SD
	7.19	0.98	8.39	0.71

P value=0.0001

showed that the mean reduction was 8.92+ 0.08mg/dl with continuous phototherapy and 9.26+0.06mg/dl with intermittent phototherapy for management of neonatal hyperbilirubinemia. The difference was found to be significant (P<0.05),[7] our findings are in agreement with this study.

However, another randomized trial showed that the mean reduction was 7.67+0.5mg/dl with continuous phototherapy and 7.03+0.03mg/dl with intermittent phototherapy for management of neonatal hyperbilirubinemia. The difference was found to be significant (P<0.05).[6] our results are not in-line with these findings.

The findings made in our study are more coherent with other previous studies.[9-12] It is line and in agreement with studies of Lau and fung which show that there is no significant difference in serum bilirubin kinetics between continuous and intermittent therapy. Additionally, according to this study intermittent phototherapy doesn't elongate the duration of therapy as Maurer and Volg stated.[10-11] Moreover other than its simplicity in application, it is also economical as the developing countries have dire need and resources are limited. Photoisomerization begins within minutes of exposure to light and bilirubin slowly migrates to the skin over hours, intermittent phototherapy regimens were hypothesized to be effective.[13-14]

CONCLUSION

Mean reduction in bilirubin level with intermittent Phototherapy was significantly higher when compared to those with continuous phototherapy for the management of neonates presenting with neonatal hyperbilirubinemia. It also confirms that as in routine, intermittent therapy is done in local setting. Through this study we also got local evidence and this is helpful to improve our practice.

REFERENCES

1. Maisels MJ, Newman TB. The epidemiology of neonatal hyerbilirubinemia. In: Stevenson DK, Maisels MJ, Watchko JF, editors. Care of the jaun-diced neonate. New York: McGraw-Hill; 2012; p.97-113.
2. Maheshwari A, Carlo WA. Digestive system disorders. In: Kliegman RM, Stanton BF, Geme JW, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Saunders Elsevier; 2011:p600-12.
3. Kumar P, Chawla D, Deorari A. Light-emitting diode phototherapy for unconjugated hyperbilirubinemia in neonates. The Cochrane Library 2011.
4. Maisels MJ, Newman TB. Prevention, screening and postnatal management of neonatal hyperbilirubinemia. In: Stevenson DK, Maisels MJ, Watchko JF, editors. Care of the jaundiced neonate. New York:McGraw-Hill;2012:p.175-94.
5. Woodgate P, Jardine LA. Neonatal jaundice: phototherapy. BMJ clinical evidence 2015;2015.
6. Niknafs P, Mortazavi A-A, Torabinejad MH, Bahman-Bijari B, Niknafs N. Intermittent versus continuous phototherapy for reducing neonatal hyperbilirubinemia. Iranian Journal of Pediatrics 2008;18:251-6.
7. Abdul-Kareem M. Comparison between continuous and intermittent phototherapy in the management of neonatal jaundice. Zanco J Med Sci 2011;15:40-4.
8. Khaliq A. Comparison of continuous with intermittent phototherapy in the treatment of neonatal jaundice. J Postgard Med Inst 2016;30(2)
9. Niknafs P, Mortazavi AA, Torabinejad MH, BijariBB, Niknafs N. Intermittent versus continuous phototherapy for reducing Neonatal hyperbilirubinemia. Iran j Pediatr 2008;18(3):251-6.
10. VolgTP, Hegyi T, Hiatt IM. Intermittent phototherapy in the treatment of jaundice in the premature infant. J Pediatr 1978;92(4):627-30.
11. Maurer HM.Controlled trail comparing agar, intermittent phototherapy and continuous phototherapy for reducing neonatal hyperbilirubinemia . J Pediatr 1973; 82(1):73-6.
12. Lau SP, Fung KP. Serum bilirubin Kinetics in intermittent phototherapy of physiological jaundice. Arch Dis Child 1984;50(9):892-4.
13. Maisels MJ, McDonagh AF. Phototherapyfor neonatal jaundice. N Engl J Med.2008;358(9):920-8.
14. Ip S, Chung M, Kulig J, et al. An evidence based review of important issues concerning neonatal hyperbilirubinemia. Pediatr. 2004;114(1):e130-e153.

INCIDENCE OF PARAPHENYLENE-DIAMINE/ KALA PATHAR POISONING IN PAKISTANI POPULATION

Urooj Husain,[1] Durdana Zafar,[2] Tufail Ahmed,[3] Pervaiz Zarif[4]

How to cite: Husain U, Zafar D, Ahmed T, Zarif P. Incidence of paraphenylene-diamine / kala pathar poisoning in Pakistani population. JAIMC. 2021; 19(1): 133-137.

Abstract

Objective: Paraphenylene-diamine (PPD) poisoning is increasing day by day in Pakistani population. This study was designed to analyze the characteristics of PPD poisoning cases.

Methodology: In this cross-sectional study, the data of 47 cases were collected from Lahore General Hospital (LGH), Lahore, during period of 2016 to 2019. The data was analyzed GraphPad Prism 5®.

Results: Out of 47 patients, 38 (80.85%) were females and 9 (19.15%) were males. During first year of the study, only six cases were reported while in succeeding years cases increases rise rapidly and reached to fifteen in last year final year of the study. Majority of the patients 16 (34%) belong to age group 20-24 years. Nearly, 85% of the patients belong to the rural areas. Moreover, the rate of PPD poisoning in married women increases alarmingly from one case in 2016 to nine cases in 2019. Almost all cases were presented with throat pain, dysphagia and edema of face and neck. More than 70 % of the patients survived after treatment.

Conclusion: The cases of PPD poisoning are increasing with rapid pace. Females of younger age group having rural background are commonly involved in PPD poisoning. Increasing number of cases in married women are alarming for the authorities and other organization to take abrupt actions. The general public awareness program should be launched in the society along with the legal restrictions from authorities about PPD/Kala Pathar sale to tackle this social and medical problem.

Key Words: Forensic medicine, toxicity, suicide, paraphenylene-diamine

Suicide is a multifarious, complicated problem and is grouped as one of the key reasons of the unnatural deaths in all ages globally. Suicide is a public health problem that requires a great attention worldwide.[1] In a single year, almost 0.8 million deaths take place worldwide. This is equal to 16 suicidal deaths per 0.1 million people. Alarmingly, 60% of the total suicides occur in Asia. In last 40 years, nearly 60% rise in suicide rates globally. The World Health Organization (WHO) estimates that if the suicidal rate continues to increase with same pace, the number of suicidal deaths will reach about 1.5 million in 2020.[2] The average suicidal rates are estimated to be higher in Asian countries as compare to the other world.[3] As far as the Pakistan is concern, in 2012, there were 13377 suicides with a rate of 7.5 suicides per 100000 people. Among these suicides, 7085 were females and 6021 were males.[4] Psychological factors and psychiatric factors play a promising role in the cause of death. In addition, there are number of suicidal related medical ailments like cancers, chronic diseases, AIDS and liver failure.[5]

Self poisoning is one of the most convenient and preferred method of suicide. However, the modes of poisoning are quite variable among localities around the world. In developed countries, people usually use drugs in high dose as poison. In developing countries, people usually use the cheap or easily available chemicals as poison for the suicide.[6] Paraphenylene-diamine poisoning (PPD) is one of

1. Urooj Husain
2. Durdana Zafar
3. Tufail Ahmedb
4. Pervaiz Zarif

1,2,4: Postgraduate Medical Institute (PGMI) Lahore, Pakistan
3. College Indus Medical College, Tando Muhammad Khan, Pakistan

Correspondence:
Dr. Pervaiz Zarif, *Department of Forensic Medicine and Toxicology, Postgraduate Medical Institute (PGMI) Lahore, Pakistan.*
Email: pervaizzarif@gmail.com

Submission Date: 12-11-2020
1st Revision Date: 21-11-2020
Acceptance Date: 29-11-2020

the most common poisons used by low socioeconomic families for committing suicide in Pakistan. Traditionally PPD is called as "Kala Pathar". Local populations are increasingly using PPD as poison. The reasons behind this increasing trend of PPD use as poison are low cost, easily available and high mortality rate. PPD is an important component of making dyes for leather, newspapers and textiles. Because of its characteristics, PPD is commonly used to dye hairs black. The small amount of PPD also uses to mix with henna for good color.[7] PPD is converted to a reactive compound called as benzoquinone diamine. This can be further converted to Brandowaski's base. This leads to anaphylaxis. The ingestion of PPD produces symptoms of various organs damage that ultimately leads to renal failure. The severity of signs and symptoms are dependent on its dose/ quantity. Generally, more than 7 grams is considered to be a lethal dose for any individual.

There is increasing use of PPD as poison in Pakistan. This study was planned to evaluate the incidence of PPD poisoning during 2016 to 2019 at Lahore General Hospital, Lahore.

METHODOLOGY

In this cross-sectional study, the retrospective data was collected from Lahore General Hospital (LGH), Lahore, is a public sector hospital providing tertiary level care of health services. LGH provides health services not only to the locals but also to people of whole Punjab provinces. The data was collected from 2016 to 2019. During this time period, a total number of 47 cases were presented of PPD poisoning in emergency department of the LGH.

The diagnosis of PPD poisoning was made either through relative's information by history or on the basis of clinical findings. The data about address/ residence, signs and symptoms, sex, socioeconomic class, and age was collected. According to their biological maturity, four groups were made (15-19 years, 20-24 years, 25-29 years, and >29 years).

The data values were presented as mean ± standard deviation of the numbers. The data was analyzed GraphPad Prism 5®.

RESULTS

During the years 2016 to 2019, a total of 47 cases were presented of PPD poisoning at LGH emergency. There were 6 cases in 2016, but the cases were increased sharply in the following years with 13, 13 and 15 cases for the year 2017, 2018, and 2019 respectively (Figure 1). Among these, 38 (80.85%) were females with mean age of 27.4±3.9, 23±3.2, 26.4±12, and 26±6.4 for the year 2016, 2017, 2018, and 2019 respectively (Figure 2). On the other side, there were 9 (19.15 %) males with mean age of 18±0, 25±8, 29±6.9, and 29±1.4 for the year 2016, 2017, 2018, and 2019 respectively (Table 1). Overall, 12.76% cases were belong to the age group 15-19 years, 34 % cases were belong to the age group 20-24 years, 25.53 % were belong to the age group 25-29 years, and 27.65 % were belong to the age group >29 years (Table 2).

Regarding marital status, 16 individuals with PPD poisoning were married. Alarmingly, in the year 2016, the cases of married person was only one, but the cases were increase sharply with 2, 4 and 9 cases in the year 2017, 2018 and 2019 respectively (Figure 3). According to the collected data, majority

Table 1: *Demographic Characteristics of the Patients*

Years	Age (Mean ± S.D)		Gender		Marital Status		Reason of Poisoning		Locality	
	Male	Female	Male (%)	Female (%)	Single (%)	Married (%)	Suicide (%)	Accidental (%)	Urban (%)	Rural (%)
2016	18±0	27.4±3.9	16.66	83.33	83.33	16.66	83.33	16.66	0	100
2017	25±8	23±3.2	23.07	76.92	84.6	15.3	92.3	7.6	15.3	84.6
2018	29±6.9	26.4±12	23.07	76.92	69.23	30.7	84.6	15.38	15.3	84.6
2019	29±1.4	26±6.4	13.33	86.66	40	60	94.7	5.2	13.33	86.66

of the PPD poisoning cases were intentionally while only few were accidental (Table 1). Moreover, nearly 85 % of the cases were from the rural areas, and nearly 15% cases were from the urban settings (Table 1). Regarding clinical signs and symptoms, nearly all cases were presented with throat pain, dysphagia, aches, and edema of face and neck.

Less than fifty percent patients were developed complications like renal and heptic damage. As far as survival rate is concerned, almost 70 percent patients survived after getting proper treatment.

Table 2: *Number of Cases According to the Age Groups*

Age Group	Number of Cases	Percentage (%)
15-19 years	06	12.76
20-24 years	16	34
25-29 years	12	25.53
. 29 years	13	27.65

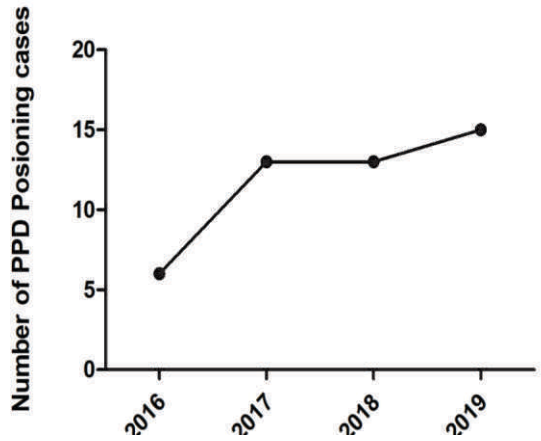


Figure 1: *Number of Cases During Four Years*

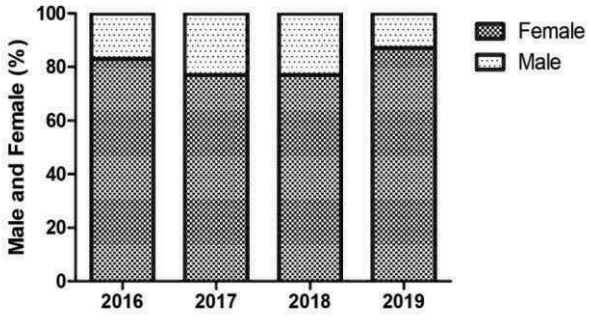


Figure 2: *Gender Ratio of the Cases in each Year*

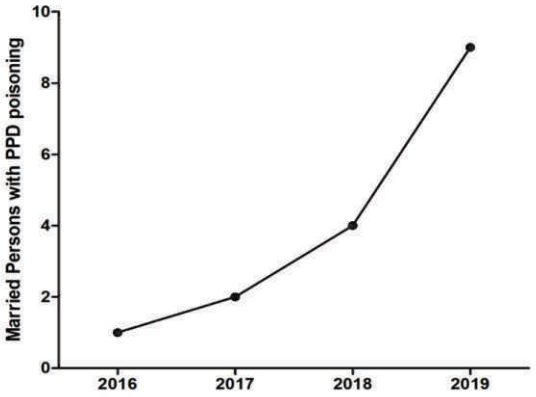


Figure3:*Number of Married Cases During Four Years*

DISCUSSION

In Pakistan, although suicide is considered as shameful act from social and religious point of view, the suicide rate has increased sharply in recent years. For this reason, suicide has become a major health problem in the society[8]. To commit suicide, people are usually looking for the chemical that is easily available. Paraphenylene-diamine poisoning (PPD)/ Kala Pathar is one of chemical that is easily available for their purpose. PPD acts like an allergen in the body and causes anaphylactic reactions, de-granulation of mast cells and hepatoranal cell damage. It directly absorbs from the mucous membranes and metabolize into substances that act as cytotoxins[9]. PPD is a compound used as constituent of the hair dyes and easily available. PPD poisoning has emerged as major mode of suicide during past years in Pakistan [10].

During the years 2016 to 2019, forty seven PPD poisoning cases were observed at LGH emergency. The numbers of cases that use PPD as poison were increasing with the succeeding years of this study. This shows emerging trend of using PPD as poison in the local population. The use of PPD as poison has also increased in the neighboring countries. Among forty seven cases, majority (80.85%) of the cases are un-married females. Similar results were observed during studies conducted in Pakistan and other countries.[11-15] This predicts the social and psychological pressure over the females in the society. As far

as their locality and economic background is concerned, majority of the cases belongs to rural background with low economic status and education. Our results are completely in line with the results from other countries where people from rural background commit more suicides than people live in urban setting.[16-18] The availability of PPD dye, gender discrimination, social pressure and illiteracy are the possible factor for the dominance of PPD poisoning in females.

Collectively, the individuals from age group 20 to 24 years dominate the number of PPD poisoning cases. This predicts younger persons are more likely to involve in suicides. This alarming situation was also observed in a study where authors study the increasing trend of suicide in young students of Pakistan[19]. Regardless of an alarmingly rising rate of suicide by young generations in Pakistan, governments and mental health experts has not addressed this issue. This should serve as a signal for the government plan to remedy the situation.

According to the data, the rates of married suicide are increasing with the time. In 2016, only one married individual commit suicide using PPD; however the number was increased to nine in 2019. Most importantly all are females. The same increasing trend of married female suicides were observed in India.[20] The main reason behind the increasing married females' suicides may be the social or cultural problems. The common practice of forced marriages in the country result in social and family pressure for the woman to stay married even in an abusive relationship; this may increase the risk of suicide in women.[21] As the PPD is commonly and cheaply available in the markets, for this reason the psychologically pressurized women are using PPD to commit suicide.

CONCLUSION

In the running days, the numbers of PPD poisoning cases are increasing and no specific antidote is available. In the current scenario, there is need to bring awareness in the general public about PPD. Moreover, there is need to regularize the sale of PPD in the market by authorities to decrease the incidences of PPD poisoning. It will be much better choice to ban PPD sale; however some non toxic alternative of PPD should be introduced to be use as dye.

Acknowledgement: None

Disclaimer: None

Conflict of Interest: The authors declare no conflict of interest

Funding Disclosure: None

REFERENCES

1. Rostami M, Jalilian A, Rezaei-Zangeneh R, Salari A: Factors associated with the choice of suicide method in Kermanshah Province, Iran. Ann Saudi Med 2016, 36(1):7-16.
2. Kordrostami R, Akhgari M, Ameri M, Ghadipasha M, Aghakhani K: Forensic toxicology analysis of self-poisoning suicidal deaths in Tehran, Iran; trends between 2011-2015. Daru 2017, 25(1):15.
3. Jordans MJ, Kaufman A, Brenman NF, Adhikari RP, Luitel NP, Tol WA, Komproe I: Suicide in South Asia: a scoping review. BMC Psychiatry 2014, 14: 358.
4. Shekhani SS, Perveen S, Hashmi DE, Akbar K, Bachani S, Khan MM: Suicide and deliberate self-harm in Pakistan: a scoping review. BMC Psychiatry 2018, 18(1):44.
5. Klonsky ED, May AM, Saffer BY: Suicide, Suicide Attempts, and Suicidal Ideation. Annu Rev Clin Psychol 2016, 12:307-330.
6. Ajdacic-Gross V, Weiss MG, Ring M, Hepp U, Bopp M, Gutzwiller F, Rossler W: Methods of suicide: international suicide patterns derived from the WHO mortality database. Bull World Health Organ 2008, 86(9):726-732.
7. Ansari RZ, Khosa AH, Yadain SM, Shafi S, Haq AU, Khalil ZH: Incidence Of Paraphenylene-Diamine Poisoning In Three Districts Headquarter Hospitals Of Pakistan. J Ayub Med Coll Abbottabad 2019, 31(4):544-547.
8. Khan MM, Mahmud S, Karim MS, Zaman M, Prince M: Case-control study of suicide in Karachi, Pakistan. Br J Psychiatry 2008, 193(5):402-405.
9. Hassan Shah F ASSaGM: Para Phenylene Diamine Poisoning: Hepatic and Renal Damage Journal of Women's Health Care 2017, 6(2):1-3.
10. Altaf Pervez Qasim MAA, Aslam Baig, Muhammad Sajjad Moazzam: Emerging Trend of Self Harm by

Using 'Kala Pathar' Hair Dye (Paraphenylene diamine): An Epidemiological Study. Annals of Punjab Medical College 2016, 10(1):26-30.

11. Bernal M, Haro JM, Bernert S, Brugha T, de Graaf R, Bruffaerts R, Lepine JP, de Girolamo G, Vilagut G, Gasquet I et al: Risk factors for suicidality in Europe: results from the ESEMED study. J Affect Disord 2007, 101(1-3):27-34.
12. Prabhakaran AC: Paraphenylene diamine poisoning. J Nat Sci Biol Med 2012, 3(2):199-200.
13. Mohamed KM HM, Aly NS: Fatal intoxications with para-phenylenediamine in Upper Egypt. Journal of Forensic Science and Pathology 2014, 17(2): 19-23.
14. Perumal S AS, Anandan H: Clinical Profile of Ingestional Hair Dye Poisoning: A Prospective Study. Int J Sci Study 2016, 4(5):154-156.
15. Javed Iqbal MH, Abid Hussain, Muhammad Bilal Ghafoor: PARAPHYLENE DIAMINE/KALA PATHAR POISONING. The Professional Medical Journal 2019, 26(5):825-830.
16. Nautiyal S TS, Ashutosh K: Pathar dye (paraphenyldiamine) poisoning: Our experience of this lethal emerging health problem in a tertiary care. Int J Otorhinolaryngol Head Neck Surg 2017, 3(4):1056-1059.
17. Elgamel AA AN: Complications and management of hair dye poisoning in Khartoum. Sudan Medical Monitor 2013, 8(3):146.
18. V. Aiswarya RAM, Bharat B. Bhanderi and Ashish Roy: Clinical profile of acute paraphenylenediamine intoxication in Egypt. Toxicol Ind Health 2010, 26(2):81-87.
19. Shakil M: A Qualitative Analysis of Suicides Committed by the Students in Pakistan. Pakistan Journal of Medical Research 2019, 58(1):35-40.
20. Radhakrishnan R, Andrade C: Suicide: An Indian perspective. Indian J Psychiatry 2012, 54(4):304-319.
21. Gururaj G, Isaac MK, Subbakrishna DK, Ranjani R: Risk factors for completed suicides: a case-control study from Bangalore, India. Inj Control Saf Promot 2004, 11(3):183-191.

ROLE OF PROBIOTICS IN WOMEN WITH RECURRENT URINARY TRACT INFECTION

Nargis Iqbal,[1] Nazia Nawaz,[2] Khulood Mukhtar,[3] Maimoona Javaid,[4] Tayiba Yousaf,[5] Mehreen Nisar[6]

How to cite: Iqbal N, nawaz N, Mukhtar K, Javaid M, Yousaf T, Nisar M. Role of probiotics in women with recurrent urinary tract infection. JAIMC. 2021; 19(1): 138-141.

Abstract

Objectives: To compare the frequency of development of urinary tract infection in women treated with oral Probiotic versus no prophylactics treatment during reproductive age with recurrent UTI.

Methodology: A Randomized control trial was conducted at Obstet/ Gynae department unit 3, Jinnah Hospital Lahore, over a period of six months. After approval from hospital ethical committee, 284 women were included in the study. They were divided into two groups 142 in each. Group A received no treatment whereas women of Group B received Probiotics. Follow up with recurrence of UTI was carried out.

Results: Mean age of the women in Group A, & B was 30.12+-6.2, & 30.26+-+-6.49 years respectively. In our study 73.2% women were married, and 27.5% unmarried. Mean BMI in Group A, & B was 32.12+-4.27 & 30.16 +-3.28 kg/m2 respectively. Development of UTI in Group B was 16.19% & in Group A was 26.76%.

Conclusions: The results of this study highlighted that Probiotics are useful for prophylaxis against recurrent UTI's.

Key Words: Probiotics, Recurrent Urinary Tract Infections

Urinary tract infection (UTI) is one of the commonest contagious health problem in women during reproductive and middle age group, the outstanding feature of UTI is its recurrence.[1] The recurrence chance after first episode of UTI is reported to be 24% in age group of 18-24 years.[2] We defined recurrent UTI as three episodes of UTI between last one year, or two episodes within last six months.[3] The most famous reason of UTI is Escherichia Coli, but numerous other bacteria or fungi can are also be responsible. The risk factors responsible for UTI are female anatomy, sexual contact, diabetes mellitus, and lack of perineal hygiene[4]. Of the women 25-30% develops recurrent infections unrelated to any functional or anatomical abnormality of the urinary tract and morbidity due to UTI is more common in women of all ages especially in middle one.[5] Therefore it is crucial to find out effective strategies and therapy for its prophylaxis to prevent recurrent infections. Probiotic play an important role in preventing recurrent UTI but limited literature is available as yet. Probiotic consist of two words "Pro" in Latin and "bios" in Greek concept is life. Elie Metchnikoff is the pioneer of Probiotics and is the winner of Russian Nobel Prize in 1907. He reported that the microbes in the Digestive system cater conducive environment and act as good contributor, especially in digestive system diseases.[6] WHO defined Probiotics as "useful living microorganism that have a positive effect on the health and physiology of a person when taken in sufficient quantities".[7] Probiotics are present in some foods or food products (in capsule, tablet & power form).The culprit bacteria could be found in probiotic food items and supplements. Probiotics should be resistant to bile and gastric acids because the said acids have to arrive in the intestines to produce useful effects on the body.[8]

1. Nargis Iqbal
2. Nazia Nawaz
3. Khulood Mukhtar
4. Maimoona Javaid,
5. Tayiba Yousaf
6. Mehreen Nisar

1-6. Department of Gynaecology, Al-Aleem Medical College/Gulab Devi Hospital, Lahore

Correspondence:
Dr. Nargis Iqbal, Al-Aleem Medical College/Gulab Devi Hospital, Lahore

Submission Date: 08-10-2020
1st Revision Date: 12-11-2020
Acceptance Date: 18-11-2020

The mode of action of probiotics could involve acidification of mucosal surface, suppression of pathogens bond, productions of vitamins, immunomodulators & the synergistic activity in collaboration with immune system of the host.[9] Some species of Lactobacillus produce hydrogen peroxide & some biosurfactants that change PH of mucosa of vagina to acidic and also has microbiomimetic regulatory effects.[10] The idea of the study was to compare the frequency of development of UTI in women treated with oral Probiotics versus no prophylactics treatment during reproductive age presenting with recurrent UTI.

METHODOLOGY

A Randomized Control Trial study was carried out in Gynae Unit-lll, Jinnah Hospital Lahore, affiliated with Allama Iqbal Medical College. The duration of study was six months from 24th October 2017 to 24th April 2018. After approval from hospital ethical committee, a total 284 women were recruited in this study by using Non probability purposive sampling technique who were fulfilling inclusion criteria (aged 20-40 years, presented with UTI and having one similar episode during the last six months. Women with renal pathology, bacterial vaginosis, on immunosuppressive therapy and lactating were omitted from the study. Informed consent was taken from all participants, demographic history was recorded and then 284 women were divided by randomly lottery method into two groups 142 in each, Group A where no treatment was given and Group B where women received Probiotic, a pack of probiotics having 30 sachets to be used one daily. Both groups were followed up every month till six months on OPD bases and women in group B were provided probiotics at each visit. To ensure compliance women were instructed to take it in front of her husband or parents and bring empty sachets to get new pack. Women giving history of UTI again during follow up period were undergone urine analysis by collecting mid-stream void in sterile container and sending it to the pathology laboratory of Jinnah Hospital Lahore. The results were collected next day and presence of UTI was noted in the Proforma, confidentiality of the data was ensured. Those women who were absent on follow up day were contacted on phone. All the data was entered & then analyzed using SPSS version 20.

RESULTS

A total of 284 women enrolled in the study were divided into two groups (A and B) 142 in each group. In Group A no treatment was given and observed conservatively, where as in Group B a pack of Probiotic having 30 sachets were given to be used daily and observed both groups on monthly bases for next six months. Mean age of the women in Group-A (Non-treatment group) was 30.12± 6.27 years & in Group B (Probiotic taken) was 30.26±6.49 years, the mean BMI of women in Group A was 32.12±4.27 and in Group B was 30.16±3.28 km/m2 as shown in Table l. In our study 73.2% women were married and 26.8% were unmarried in Group A, where as in Group B 72.5% were married and 27.5% were unmarried as shown in Table ll. The Table lll and lV depicted the development of urinary tract infection in both groups in relation with age and parity.

DISCUSSION

Table 1: *Age and BMI of Women (n=284)*

Age (Years) Groups	Mean	Standard Deviation
Group A (Non treatment)	30.12	6.27
Group B (Probiotic taken)	30.26	6.49
BMI (kg/m²)		
Group A (Non treatment)	32.12	4.27
Group B (Probiotic taken)	30.16	3.28

Table 2: *Marital Status and Parity (n=284)*

Marital Status	Group A (Non treatment)	Group B (Probiotics taken)
Married	104 (73.2 %)	103 (72.5 %)
Un-Married	38 (26.8 %)	39 (27.5 %)
Parity		
Para – 1	30 (21.1 %)	26 (18.3 %)
Para – 2	22 (15.5 %)	23 (16.2 %)
Para – 3	23 (16.2 %)	24 (16.9 %)
Para – 4	12 (08.5 %)	12 (08.5 %)
Para – 5	17 (12.0 %)	18 (12.7 %)

Table 3: Development of UTI with Age (n=284)

Groups	Development Yes	Of UIT No	P-Value	Chi Square
Group B	23	119	0.030	4.697
Group A	38	104		
Age Years (20-30)				
Group B	10	61	0.391	0.735
Group A	14	58		
(31-40)			0.031	
Group B	13	58		4.648
Group A	24	47		

Table 4: Development of UTI With Parity (n=284)

Parity	Development Yes	Of UTI No	P – Value	Chi Square
Para-1 Group B	4	22	0.073	3.217
Group A	11	19		
Para - 2 Group B	3	20	0.396	0.721
Group A	5	17		
Para-3 Group B	5	19	0.671	0.181
Group A	6	17		
Para – 4 Group B	2	10	0.615	0.253
Group A	3	9		
Para- 5 Group B	3	15	0.208	1.588
Group A	6	11		

Urinary tract infection is one of commonest bacterial infection in women and 50% to 60% of adult women experience a UTI in their life time.[11] The bacterium can grow in anywhere in the urinary tract including urethra, bladder, ureter or kidneys.[12] In the developing countries like Pakistan, India, Bangladesh, Afghanistan, and in tropical developed countries UTI is the main cause of morbidity and mortality in children and adults.[13] The incidence of UTI is 3% to 8% in girls and 1% of boys in developed and higher incidence has been reported in the developing countries.[14] The bacteria that is notorious for UTI is E. coli, but others like Staphylococcus, Pseudomonas, Klebsiella, E.faecallis and Proteus Vulgaris are also responsible for recurrent UTI especially in females.[15,16] In our study, mean age of the women in Group A was 30. 12 +-6.27 years & in Group B was 30.26 +- years. BMI play an important role in UTI especially in females, greater the BMI greater the chances of having recurrent UTI's. In this study the mean BMI in Group A was 32.12 & in Group B was 30.12 kg/m^2, these findings are similar with other studies[17,18]. Sexual contact and multiple sexual partners are responsible for UTI and its recurrence, in this study 73.2% women were married and 26.8% were unmarried in Group A, whereas in Group B 72.5% women were married and 27.5% were unmarried, these observations are tallying with other studies.[19,20] Lactobacillus is a probiotic, well known for the prevention of UTI can be given orally or vaginally, it create hostile environment for urinary microorganism in urine[21]. In our study the development of UTI in Group B (Probiotic group) women was only 16.19% whereas in Group A (Conservative group) it was 26.76%, the P-Value was 0.030 and Chi Square 4.697, this result was highly significant and consistent with other studies[22, 23, 24]. Increasing age is more prone for the development of UTI as compare to younger women, in this study women between 31-40 year and in Group A 16.9% develop UTI as compare to Group B only 9.1% women develop UTI in same age group, the P-value was 0.031 which is markedly significant and this is tallying with other studies.[25,26] Literature revealed that increasing parity was not markedly associated with UTI as in this study results showed that UTI's are evenly distributed among women of all groups of parity and these findings are similar with other studies.[18,27,28]

CONCLUSION

Urinary tract infection is quite common both in developed and underdeveloped countries, with a higher incidence rate in female population. The results of this study highlighted that Probiotics are useful for prophylaxis against recurrent UTI's.

REFERENCE

1. Foxman B, Brown P. Epidemiology of urinary tract infections: transmission and risk factors, incidence and cost. Infect Dis Clin North Am 2003;17:227-241.
2. Foxman B, Gillespie B, Koopman J, Zhang L, et al. Risk factors for second urinary tract infection among college women. Am J epidemiol 2010; 151: 1194-201.

3. Albert X, Huertas I, Pereiro ll. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. Cochrane Database Syst Rev 2004; CD001209.
4. Hummers-Pradier E, Kochen MM. Urinary tract infections in adult general practice patients. Br J Gen Pract.2002;52(482)752-761.
5. Tandogdu Z, Wagenlehner F. Global epidemiology of urinary tract infections. Curr Opin Infect Dis. 2016; 29:73-79.
6. Donders GG. Microscopy of the bacterial flora on fresh vaginal smears. Infect Dis Obstet Gynecol 1999; 7:177-179.
7. Reid G, Dols J, Miller W. Targetting the vaginal microbiota with probiotics as a means to counteract infections. Curr Opin Clin Nutr Metab Care 2009; 12:583-587.
8. Preidis Geoffrey A, Versalovic J. Targeting the human Microbiome with antibiotics, probiotics, and prebiotics: gastroenterology enters the metagenomics era. Gastroenterology 2009;136:2015-2031.
9. Iannitti T, Palmieri B. Therapeutical use of probiotic formulations in clinical practice. Clinical Nutricion 2010;29:701-725.
10. Kaur IP, Chopra K, Saini A. Probiotics: Potential pharmaceutical applications. Eur J Pharm Sci 2002; 15:1-9.
11. Al-Jiffri O, El-Sayed Z, Al-Sharif F. Urinary tract infection with Escherichia coli and antibacterial activity of some plants extracts. Int J Microbiol Res. 2011;2:1-7.
12. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008; 36:309-322.
13. Abraham G, Varughese S, Thandavan T, et al. Chronic kidney disease hotspot in developing countries in South Asia. Clin Kidney J.2016;9:135-141.
14. World Health Organization. Urinary tract infections in infants and children in developing countries in the context of IMCI.No.WHO/FCH/CAH/05.11. Geneva, Switzerland: WHO;2005:45-50.
15. Mody L, Juthani-Mehta M. Urinary tract infections in older women: a clinical review. JAMA 2014; 311: 844-854.
16. Dubey D, Padhy RN. Antibacterial activity of Lantana Camara L. against multidrug resistant pathogensfrom ICU patients of a teaching hospital. J Herb Med.2013;3:65-75.
17. Aslam S, MD, Albo M, MD, Brobaker L, MD. Recurrent urinary tract infection in adult women. JAMA 2020;323(7):658-659.
18. Shaheen G, Akram M, Jabeen F, Munir N, et al. Therapeutic potential of medicinal plants for the management of urinary tract infection: A systematic review. Clin Exp Pharmacol Physiol.2019;46:613-624.
19. Bolton M, Van Der Straten A, Cohen CR. Pro biotics: potential to prevent HIV and sexually transmitted infections in women. Sex Transm Infect 2008; 35:214-225.
20. Aragon IM, Herrera-Imbroda B, Queipo-Ortuno MI, Castillo E, et al. The Urinary Tract Micro-biome in Health and Disease. Eur Urol Focus 2018;4:128-138.
21. Grin PM, Kowalewska PM, Alhazzan W, Fox-Robichaud AE, Lactobacillus for preventing recurrent urinary tract infections in women: meta-analysis. Can J Urol. 2013;20:6607-6614.
22. Amdekar S, Singh V, Singh DD. Probiotic therapy: immunomodulating approach toward urinary tract infection. Curr Microbiol. 2011;63:484-486.
23. Reid G, Dols J, Miller W. Targeting the vaginal microbiota with probiotics as a means to counteract infections. Curr Opin Clin Nutr Metabol Care. 2019; 12:583-587.
24. Barrons R, Tassone D. Use of Lactobacillus probiotic for bacterial genitourinary infections in women: a review. Clin Ther 2008;30:453-468.
25. Costantini E, Giannitsas K, Illiano E. The role of non-antibiotic treatment of community acquired urinary tract infection. Curr Opin Urol 2017;27:120-126.
26. Komal S, Kazmi SA, Khan JA, Gilani MM. Antimicrobial activity of Prunella Vulgaris extracts against multi-drug resistant E coli from patients of urinary tract infection. Pak J Med Sci 2018;34:616-620.
27. Reid G, Bruce AW. Probiotic to prevent urinary tract infections: the rationale and evidence. World J Urol 2006;24:28-32.
28. Pervaiz S, Malik KA, Ah Kang S, Kim HY. Probiotics and their fermented food products are beneficial for health. JPMA 2006;10:1171-1185.

FREQUENCY OF VARIOUS METERNAL & FETAL RISK FACTORS FOR EARLY ONSET NEONATAL SEPSIS-AN EXPERIENCE IN A TERTIARY CARE HOSPITAL

Sonia Zofishan,[1] Ayesha Arif,[2] Muhammad Ashraf Zia,[3] Muhammad Imran[4]

How to cite: Zofishan S, Arif A, Ziaa MA, Imran M. Frequency of various maternal & fetal risk factors for early onset neonatal sepsis – anexperience in a tertiary care hospital. JAIMC. 2021; 19(1): 142-146.

Abstract

Background: Medical literature defines early-onset sepsis (EOS) as blood or cerebrospinal fluid bacterial infection which is proven on culture occurring in the 1st week of life i.e., 1st to 7th day of life in a newborn. This disease has a high sequelae and aftermath. Neonatologist and doctors all around the world try to pick this infection in its initial days of presentation in neonates and also identify those at the risk of developing it; so that a prompt medical treatment can be initiated timely and life-threatening consequences of early onset sepsis can be prevented by the administration of antibiotics.

Objectives: To assess the frequency of various risk factors which can lead to early onset sepsis.

Methodology: Cross-sectional type of study done at the Neonatal Nursery Unit NNU of the Department of Paediatrics, Jinnah Hospital, Lahore for 7 months [1st June till 31st December 2018] .A total of 150 neonates fulfilling the inclusion criteria were enrolled. All the maternal and fetal risk factors were evaluated and entered in a questionnaire. Data from the questionnaire was entered in SPSS version 17 for analysis.

Results: Among maternal factors, PROM was seen in 95(63.3%) followed by maternal fever (51.3%) and chorioamnionitis (20%). Among fetal risk factor prematurity was seen in (50.7%) followed by thrombocytopenia (32.7%), low birth weight (27.3%) and leukocytosis (19.3%).

Conclusion: Among maternal factors, the highest factor was of premature rupture of membranes (63.3%) and the highest fetal risk factor was prematurity (50.7%).Reducing the risk of these factors can help to reduce the risk of early onset sepsis.

Key Words: Neonatal Sepsis, low birth weight, prematurity, premature rupture of membranes, maternal fever, chorioamnionitis, thrombocytopenia, leukocytosis

Neonatal sepsis is a globally accepted issue of public health concern and a leading cause of death in both term and preterm infants.[1] Centers for Disease Control and Prevention define Neonatal early-onset sepsis as blood and/or cerebrospinal fluid infection which is proven on culture presenting in the newborn at less than one week of age i.e., at less than 7 days of age.[2] Whereas, in the case of very low birth weight (birth weight <1,500 g) infants who are admi-tted in hospital for treatment and medical interven-tion, early onset sepsis is taken as infection which is proven on culture presenting at less than 3 days of life i.e., less than 72 hours of age.[3]

The major toll of death from early onset sepsis in neonates is in the developing countries which is 6 times higher than that of the developed countries. The neonatal mortality rate has been recorded to be 30/1,000. This amounts for around 4 million deaths every year. Developing countries account for 95% of these deaths.[4] There is a study done by Parez et al in which he evaluated factors linked with the risk of developing early onset sepsis in neonates. The factors he found to have an association with the early

1. Sonia Zofishan
2. Ayesha Arif
3. Muhammad Ashraf Zia
4. Muhammad Imran

1,2. *Department of Paediatrics, Jinnah Hospital, Allama Iqbal Medical College, Lahore*
3. *Department, ICU & Pain Management, Jinnah Hospital, Allama Iqbal Medical College, Lahore*
4. Department of Pathology, Jinnah Hospital, Lahore /Allama Iqbal Medical College, Lahore

Correspondence:
Dr. Sonia Zofishan, *Department of Paediatrics, Jinnah Hospital, Lahore/Allama Iqbal Medical College, Lahore*
Email: herewegodoctors@yahoo.com

Submission Date: 13-11-2020
1st Revision Date: 10-12-2020
Acceptance Date: 17-12-2020

onset sepsis related to mother were age of mother ≤ 15 years (OR 3.50; 95% CI 1.56-7.85), rupture of membranes in mother >18 h (OR 2.65; 95% CI 1.18-5.92), fever in mother (OR 6.04; 95% CI 1.54-23.6).The factors among neonates to have as association with early onset sepsis were birth weight of newborn ≤2,500 g (OR 4.82; 95% CI 2.38-9.75) and gestational age <37 weeks (OR 3.14; 95% CI 1.58-6.22). [5]

Neonatal mortality rate recorded for Pakistan is 49 per 1000 live births. Worldwide neonatal deaths are due to early onset sepsis or due to delivery complications Pakistan has a major share of 7% of neonatal deaths world-wide and out of these 36% are due to infec-tion.[6,7] Jinnah Hospital Lahore is a tertiary care hos-pital where patients from all over Punjab are being treated. Rationale of the study is identifying the frequency of common risk factors prevailing in this hospital to help in early recognition of preventable factors and in reducing the neonatal mortality rate. Henceforth help to achieve the Millennium Development Goal for child survival.

Risk factors: Following risk factors associated with EOS were included in the study:

Maternal risk factors

1. **Chorioamnionitis:** determined on clinical findings fever (temp: 99.60 F), tenderness in fundus of uterus, tachycardia in mother (>100/min), fetal tachycardia (>160/min) and purulent ,meconium stained or foul smelling amniotic fluid .
2. Premature rupture of membranes (PROM) > 48 hours assessed on history (vaginal examination by checking the rupture of membranes present on obstetric record).
3. Maternal fever > 38°C, 15 days before delivery.

Fetal risk factors

1. Low birth weight < 1500 grams
2. Leukocytosis (>26,000/cm3).
3. Pre-maturity <34 weeks determined on obstetrics history or LMP.
4. Thrombocytopenia (150,000/cm^3).

Neonatal early-onset sepsis is defined as any neonate presenting within 72 hours of life with common symptoms that include listlessness, laziness, hypothermia(96°F), reluctance to feed and has a positive blood culture with bacterial infection(105 colony count/HPF).

METHODOLOGY

At the Neonatal Nursery Unit NNU of the Department of Paediatrics, Jinnah Hospital after approval by the institutional ethical review committee, a cross sectional study was done for a period of seven months(1st June to 31st Decmber 2018). Non-Probability consecutive sampling technique was used. Keeping confidence interval as 95%, margin of error as 8% a sample size of 150 cases was calculated and expected percentage of PROM as 41%.[8] 150 inborn neonates of both genders delivered at Jinnah Hopsital, Lahore up to 7 days of life having sepsis were included after taking infor-med consent from parents. Babies born at home or other hospitals and those with congenital malforma-tions determined on clinical examination were excluded. Doctors, nurses, paramedical staff and parents attending the patients were advised to observe the barrier nursing protocols strictly. Patients' particulars like name, age, weight, gender were entered in the Proforma by researcher. Immediately after admi-ssion patients who fulfill the inclusion criteria; their blood sample for culture were taken and sent to Pathology Emergency laboratory of Jinnah Hospital, Lahore. All the maternal risk factors like chorio-amnionitis, PROM, maternal fever and fetal risk factors like low birth weight, leukocytosis, throm-bocytopenia and prematurity were evaluated and entered in a structured Proforma. Effect modifiers like age, gender were addressed by stratification of data. Data from the questionnaire was entered in SPSS version 17 for analysis. Nume-rical variables which include maternal age, weight of new born were shown as mean and standard deviation. Qualitative variables which here imply gender, chorioamnionitis, PROM, maternal fever and fetal risk factors like low birth

weight, and prematurity were shown as frequencies and percentages. Strati-fication of data was done for maternal age, baby gender and birth weight to sort out the issue of effect modifiers. p-value ≤ 0.05 was taken as significant and after the stratification of variables Chi-square test was applied.

RESULTS

Mean age of the mothers was 29.15 ± 7.35 years with minimum and maximum age as 18 and 44 years. There were 86(57.3%) whose age was 18-29 and 64(42.7%) mothers had 30-44 years of age. The mean age of babies was 1.68 ± 1.57 with minimum and maximum age of 1 and 7 days. There were 86(57.3%) and 64(42.7%) female babies. There mean birth weight of babies was 1.97 ± 0.68 kg. PROM was seen in 95(63.3%), 77(51.3%) had maternal fever and 30(20%) were diagnosed with chorioamnionitis. A total of 41(27.3%) cases who had low birth weight, leukocytosis were seen in 29(19.3%) of the cases, 76(%) had prematurity and 49(32.7%) cases had thrombocytopenia. When data was stratified for maternal age, neonatal gender and LBW, we found significant association in Gender versus low birth weight, prematurity versus low birth weight, p-value < 0.05.(Table 1,2,3)

Table 1: Frequency Distribution of PROM > 48 Hours

		Frequency	Percentage
PROM> 48 hours	**Yes**	95	63.3%
	No	55	36.7%
	Total	150	100.0%

Comparison of PROM with respect to maternal age groups

		PROM		Total
		Yes	No	
Age groups (years)	**18-29**	51	35	86
		53.7%	63.6%	57.3%
	30-44	44	20	64
		46.3%	36.4%	42.7%
Total		95	55	150
		100.0%	100.0%	100.0%

Chi-square = 1.410
P-value = 0.235

DISCUSSION

EOS most commonly presents on the first day of life. It is a catastrophic, rigorous infection attacking all the systems of the body vigorously acquired by perinatal transmission from the mother during the period immediately before and after the birth of a baby[9]. In current study the mean age of mothers was 29.15 ± 7.35 years with minimum and maximum age as 18 and 44 years. The mean age of babies was 1.68 ± 1.57 with minimum and maximum age of 1 and 7 days. There were 86(57.3%) and 64(42.7%) female babies. There was a study done on 192 infants, its reports showed that, the males were 100 (52.1%) and the females were 92 (47.9%).[10]

Table 2: Frequency Distribution of Maternal Fever

		Frequency	Percentage
Maternal fever	**Yes**	77	51.3%
	No	73	48.7%
	Total	150	100.0%

Table 3: Frequency distribution of Pre-maturity

		Frequency	Percentage
Pre-maturity	**Yes**	76	50.7%
	No	74	49.3%
	Total	150	100.0%

Factors in mothers which lead to a risk of developing early onset sepsis include preterm labour and delivery, infection of birth canal, purulent foul smelling meconium-stained vaginal discharge, colonization with group B streptococcus (GBS), prolonged rupture of membranes, chorioamnionitis, and maternal fever in the last trimester or at the time delivery. In current study the mean birth weight of babies was 1.97 ± 0.68 kg. There is one more study in literature, the results of this study showed that the average age is 4 (1–28) days and the average birth weight 3050 g (2290–3450 g)10.Gestational age average is found to be 38 (36.6–38) weeks.[10] The cases of the premature delivery are 38 (19.8%) and the cases of full-term delivery are 154 (80.2%).[10]

At the time of delivery risk factors found in

mother include premature rupture of membranes, fever, vaginal colonization with group B streptococcus (GBS), and Group B Streptococcal bacteriuria. In current study PROM was seen in 95(63.3%). A study reported that among 7 cases of sepsis 3(42.85%) cases had PROM[11]. We found that 77(51.3%) had maternal fever as another study found a total of 14.28% cases had maternal fever.[11] We found that 30(20%) were diagnosed with chorio-amnionitis. In a study done at Agha Khan University in neonates with sepsis duration of PROM > 48 hours was present in 41%, maternal fever was present in 88%, chorioamniontis was found in 71%, gestational age < 34 weeks was present in 41% and LBW< 1500 grams was present in 47% and leuko-cytosis was present in 41% and thrombocytopenia in 59%.[8] The findings of our study and all studies discussed here are comparable.

Furthermore, on the other hand factors in infants which are linked to a risk of developing early-onset sepsis include prematurity/low birth weight, congenital anomalies, complicated or instrument-assisted delivery, and low APGAR scores (score of 6 at 5 min)[12,10]. Sick premature infants who are hospitalized in nursery or intensive care settings for vigilant observation and medical intervention have to undergo various invasive procedures, skin pricks, intravenous cannulation, nasopharyngeal intubation, endotracheal intubation; in such sick babies the protective barrier function of the skin and mucus membranes lining the orifices is abated and compromised.[13] Apart from these, other socioeconomic, cultural and community related factors associated with early onset sepsis include unbooked mothers, no proper booking visits during the preganancy, lack of access to a well-equipped maternity delivery suite, inadequate diet of mother, poverty, poor hygiene, mother using illegitimate drugs of abuse, male sex, and African American mother (higher rate of GBS colonization).[13] In this study a total of 41(27.3%) cases that had low birth weight. Leuko-cytosis was seen in 29(19.3%) of the cases. It was seen that 76(%) had prematurity Very low birth weight (VLBW) preterm neonates have a grave risk and propensity of developing early onset sepsis. The risk is ten folds and of those Very low birth weight neonates who develop early onset sepsis more than one third die.[14] Extremely low birth weight neonates (<1000g, ELBW) are much more assailable and susceptible to develop EOS. More so Early onset sepsis accounts for more than 50% deaths among extremely low birth weight neonates within the first 2 days of life[15]. We found that 49(32.7%) cases had thrombocytopenia. We did not find APGAR score and other factors discussed in above study and other findings are compareable with above study.

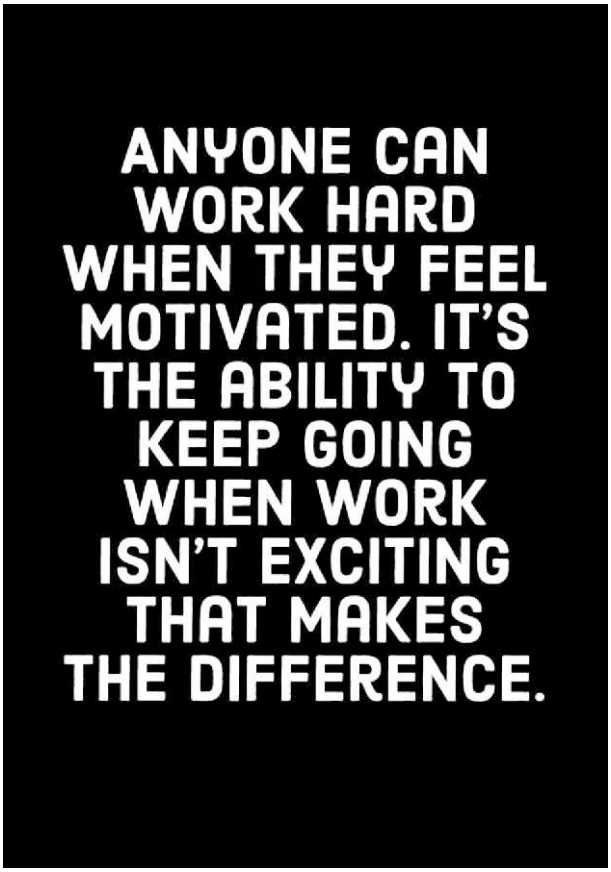
CONCLUSION

In the maternal risk factors, the highest frequency was seen in premature ruptures of membrances 95(63.3%) followed by maternal fever (51.3%) and chorioamnionitis (20%). Among fetal risk factor the highest risk was prematurity (50.7%) followed by thrombocytopenia (32.7%), low birth weight (27.3%) and leukocytosis (19.3%). By reducing the risk of these factors we can help to reduce the risk of early onset sepsis.

REFERENCES

1. Camacho-Gonzalez A, Spearman PW, Stoll BJ. Neonatal infectious diseases: evaluation of neonatal sepsis. Pediatr Clin North Am 2013;60(2):367-89.
2. Mukhopadhyay S, Puopolo KM, editors. Risk assessment in neonatal early onset sepsis. Seminars in perinatology; 2012: Elsevier.
3. Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005–2008. Pediatr Infect DiS J 2011;30(11):937-41.
4. Edmond K, Zaidi A. New approaches to preventing, diagnosing, and treating neonatal sepsis. PLoS Med 2010;7(3):e1000213.
5. Pérez R, Lona J, Quiles M, Verdugo M, Ascencio E, Benítez E. Early neonatal sepsis, incidence and associated risk factors in a public hospital in western Mexico. Rev Chilena Infectol 2015;32(4):387-92.
6. Bhutta ZA. Maternal and child health in Pakistan: challenges and opportunities: Oxford University Press, USA; 2004.

7. Jalil F. Perinatal health in Pakistan: a review of the current situation. Acta Paediatr 2004;93(10):1273-9.
8. Alam MM, Saleem AF, Shaikh AS, Munir O, Qadir M. Neonatal sepsis following prolonged rupture of membranes in a tertiary care hospital in Karachi, Pakistan. J Infect Dev Ctries 2014;8(01):067-73.
9. Nizet V, Klein JO. Bacterial sepsis and meningitis. Infectious Diseases of the Fetus and Newborn Infant 7th ed Philadelphia, PA: Elsevier 2011:222-75.
10. Xiao T, Chen L-P, Liu H, Xie S, Luo Y, Wu D-C. The Analysis of Etiology and Risk Factors for 192 Cases of Neonatal Sepsis. BioMed Res Int 2017; 2017: https://doi.org/10.1155/2017/8617076.
11. Hsha C, Adlin RC. Is there any association between maternal risk factors and early neonatal sepsis? Int J Biomed Res 2016;7(8):558-67.
12. Benitz WE, Gould JB, Druzin ML. Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. Pediatrics 1999;103(6):e77-e.
13. Arnon S, Litmanovitz I. Diagnostic tests in neonatal sepsis. Curr Opin Infect Dis 2008;21(3):223-7.
14. Stoll BJ, Hansen NI, Higgins RD, Fanaroff AA, Duara S, Goldberg R, et al. Very low birth weight preterm infants with early onset neonatal sepsis: the predominance of gram-negative infections continues in the National Institute of Child Health and Human Development Neonatal Research Network, 2002–2003. Pediatr Infect Dis J 2005;24(7):635-9.
15. Adkins B, Leclerc C, Marshall-Clarke S. Neonatal adaptive immunity comes of age. Nat Rev Immunol 2004;4(7):553.



CARDIOPULMONARY BYPASS TIME: A PREDICTOR OF MYOCARDIAL DAMAGE IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING

Usman Javed Iqbal,[1] Nasir Iqbal,[2] Muhammad Ijaz Bhatti,[3] Muhammad Abrar Hussain,[4] Rajia Liaqat,[5] Muhammad Bilal[6]

How to cite: Iqbal UJ, Iqbal N, Bhatti MI, Liaqat MA, Bilal M. Cardiopulmonary bypass time: a predictor of myocardial damage in patients undergoing coronary artery bypass grafting. JAIMC. 2021; 19(1): 147-150.

Abstract

Objective: To measure the effect of cardiopulmonary bypass time on myocardial damage in terms of postoperative cardiac enzymes levels particularly Creatine phosphokinase (CK) and Creatine kinase-MB.

Methodology: It was a prospective study of 100 patients undergoing CABG for the first time. Data was collected using a questionnaire for demographic features and perioperative variables. Study population was divided into 2 groups for comparison: patients with CPB time≤ 90 minutes and others with CPB time >90 minutes). Postoperative cardiac enzyme levels were evaluated with respect to CPB time. Two groups were compared based on their means by using Independent sample t-test and ap-value of ≤0.05 was considered as statistically significant.

Results: There was an overall male predominance with mean age of patients being56.7±9.2 years. A significant relationship between CPB time with postoperative cardiac enzyme (CK& CKMB) levels was found as p values were < 0.05 (significant) for both cardiac markers however the relationship between CPB time and CKMB lost its significance at postoperative day 3 as p value was 0.70 which is insignificant.

Conclusion: Patients with CPB time > 90 minutes were having more myocardial damage in terms of raised cardiac biomarkers as compared to those with CPB time ≤90 minutes.

Key Words: Myocardial injury, Postoperative MI, Cardiac biomarkers, Creatine kinase.

Coronary artery bypass grafting (CABG), using cardiopulmonary bypass (CPB) is a common procedure, associated with a mortality rate of <2%in elective cases.[1] During surgey thoracic aorta is cross clamped at ascending aorta level to provide dry operative field for better operative visibility. However this increases the risk of ischemic injury to vital organs. These complications depend not only on duration but also on pathophysiological and hemodynamic perturbations resulting from CBP & aortic cross clamping.[2] In addition, cardioplegia can also have negative impact on myocardial function including myocardial stunning.[3,4]

Perioperative myocardial cellular damage is a major problem during CABG leading to leakage of proteins from these cells. These proteins vary in their release patterns and their cardiospecificity.[5] Historically, most commonly used markers of myocardial necrosis post operatively, are Creatine kinase (CK) and creatine kinase-MB (CK-MB).[6] However, the time lag between surgical damage and detection of quantifiable values of these proteins renders rapid evaluation of myocardial injury very difficult.[7]

The main objective of this study was to measure postoperative cardiac enzyme levels after CABG and to look for possible relation of these enzymes

1. Usman Javed Iqbal
2. Nasir Iqbal
3. Muhammad Ijaz Bhatti
4. Muhammad Abrar Hussain
5. Rajia Liaqat
6. Muhammad Bilal

1. *Clinical (Cardiac) Perfusionist / Gulab Devi Teaching Hospital Lahore*
2. *Azra Naheed Medical College, Lahore*

3-6. *Gulab Devi Teaching Hospital Lahore*

Correspondence:
Dr. Usman Javed Iqbal, *Clinical Perfusionist / Assistant Professor; Gulab Devi Teaching Hospital Lahore*
E-mail: sh.usmanjavediqbal@gmail.com

Submission Date: 18-11-2020
1st Revision Date: 24-11-2020
Acceptance Date: 30-11-2020

with CPB time.

METHODOLOGY

Using non probability (purpo-sive) sampling 100patients undergoing CABG in a tertiary care hospital were selected. It was a prospec-tive longitudinal study with three days follows up after surgery.

All patients with age 30 years and above; regardless of the gender, who underwent CABG were included in the study. Patients with Redo surgery, as well as all those patients with baseline renal function impairment, muscular dystrophy, myositis &/or operated off bypass were excluded.

Data collection methods: All surgeries in study population were done using recommended hypo-thermia, cold antegrade cardioplegia and cardio-pulmonary bypass. Labs were followed up for three post op days. Using short structured questionnaire, basic demographic details, postoperative CK& CK-MB levels and other related parameters were noted. Details of common conventional risk factors for CAD were also obtained.

Study population was divided into two groups: those with CPB time ≤ 90 min and those with CPB time > 90 min.Statistical Package for Social Sciences (SPSS) version 20.0 was used for descriptive and inferential analyses. Categorical data was presented either as percentages or as graphs whereas qualitative analysis was presented as descriptive and frequency distribution. Mean values of two groups were compared using independent statistical t-test. A p-value of ≤0.05 was considered as significant.

Reference values of the enzyme levels were considered according to the institutional protocols and previous literature.[8]

RESULTS

The mean age of patients was 56.7±9.2 with a male predominance (80% males). Of all patients 55 had diabetes and66 were hypertensive. Whereas 26 of those were smokers, 26 also had a strong family history of coronary artery disease.

Table.01 shows overall characteristics of study population variables as under:

Table.02 shows the comparison between the two groups with respect to cardiac biomarkers for three successive postoperative days.

Patients with CPB time ≤90 minutes had mean blood CK levels of 959.8 ± 91.2, 914 ± 99.5 and 1176±120.7 IU/L for days 1 to day 3 respectively.

Table 1: *Descriptive Statistics of Patient Height, Weight, BSA & Other Peri-op Variables*

	MEAN±S.D
Height (cm)	165.3±11.96
Weight (kg)	72.5±13.5
BSA (kg/m^2)	1.75±2.4
Pump Flow (lit/min)	4.1± 1.7
Bypass time (min)	97.51±45.1
Perfusion Pressures (mmHg)	60.5±8.8
Urine output (lit/min)	1.51±0.544

Whereas those with CPB time >90 minutes, had mean CK values of 1004.2±84.5, 1091±121.5 and 1814±189 for days 1 through day 3 respectively.

Table 2: *Comparison Between the Two Groups in Different Postoperative Days with Respect to CPK & CKMB Levels*

		CPB TIME ≤ 90 MIN	CPB TIME >90 MIN	P-value
		MEAN ± S.D	MEAN ± S.D	
DAY-1	CK (IU/L)	959.8± 91.2	1004.2±84.5	0.002
	CKMB (IU/L)	45.5±15.1	55.7±19.1	0.01
DAY-2	CK (IU/L)	914.3±99.5	1091±121.5	0.02
	CKMB (IU/L)	58.4±20. 6	7B.3±1B.6	0.04
DAY-3	CK (IU/L)	1176±120.7	1814±189.1	0.04
	CKMB (IU/L)	60.9±22.3	70. 8±30.4	0.70

Calculated p-values of 0.002, 0.02 and 0.04 for all these respective days were statistically significant with respect to CK levels.

Similarly for serum CKMB, patients with CPB time ≤ 90 minutes had mean serum CKMB levels 45.5±15.1, 58.4±20.6 and 60.9±22.3 IU/L. For patients with time >90 minutes mean serum CKMB levels were 55.7±19.1, 78.3±186 and 70.8±30.4 IU/L respectively for three successive post op days. p-values were 0.01, 0.04 for postoperative day 1 and day 2however the difference between both groups i.e

CPB time ≤ 90 min and CPB time >90min (with respect to CKMB)was lost at postoperative day 3 as p value was 0.70 which is insignificant.

DISCUSSION

Overall our study shows a significant relationship between CPB time (≤ 90 and >90) with postoperative cardiac enzyme levels (CK& CKMB) as p-value is significant (≤0.05) for both cardiac markers. The literature review shows results consistent with our study. Prognostic significance of creatine kinase MB (CK-MB) or troponin elevation within 24 hours after CABG was reported by Domanski et al[9]. Work by Costa et al showed that patients undergoing CABG had increase in CK-MB levels (42.9%) of up to 3 times. Also worth mentioning is that CK-MB may also be detectable after surgical skeletal muscle injury and intraoperative cardiac manipulation. Similarly rise in CK-MB levels may also occur in absence of permanent myocyte damage.[10]

In the GUARD during Ischemia Against Necrosis (GUARDIAN) study, post CABG CK-MB levels of <1 ×, >5 ×, >10 ×, and >20 × ULN, respectively, had a six-month mortality of 3.4%, 5.8%, 7.8%, and 20.2% respectively (p = 0.0001)[11]. An elevated CK-MB of 3× normal after intervention should be managed like non interventional non-Q-wave MI patients as suggested b y some studies.[12]

Work by Ramsay et alon on 800 patients revealed 10 times higher mortality and left ventricular dysfunction for CK-MB levels of 100 ng/mL or higher as compared to those with values less than 25 ng/ml, with findings being equally impressive even after one year.[13] Results of these studies are in agreement with that of our study. However, Conflicting results can also be found between the previous investigations; mainly because different studies employed different markers of cardiac injury. Older studies (using less-sensitive tests) that evaluated patients with ischemia during stress testing did not show elevations in troponins or other biomarkers and thus did not support the hypothesis. It is noteworthy, however, that because of relatively high specificity, CK-MB was the preferred marker of cardiac injury for many years before current generation sensitive assays became available. CK-MB rises four to six hours after the infarction but may take up to 12 hours as suggested by Robinson & Christenson.[14] Based on literature review and finding of study we may infer that cardiac enzymes levels colligate with CPB time duration and may serve as important predictor of myocardial damage.

Study limitations. Study biomarkers were measured only on the first three postoperative days so myocardial damage evolving later than the third postoperative day might have been missed because our study protocol. This question may partially be answered by the fact that majority (80%) of postoperative MI occur in the first two post op days.[15,16,17]

CONCLUSION

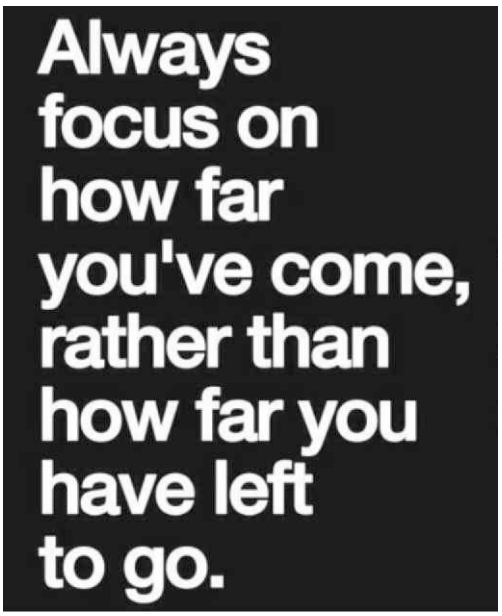
We concluded that patients with CPB time > 90 minutes were having more myocardial damage in terms of raised cardiac biomarkers as compared to those with CPB time ≤ 90 minutes. So CPB time may serve as an important predictor of myocardial damage.

REFERENCES

1. Buffolo E, de Andrade CS, Branco JN, Teles CA, Aguiar LF, Gomes WJ. Coronaryartery bypass grafting without cardiopulmonary bypass. Ann Thorac Surg 1996;61:63–6.
2. Gelman S. The pathophysiology of aortic cross-clamping and unclamping. Anesthesiology. 1995; 82(4): 1026-57.
3. Pfister AJ, Zaki MS, Garcia JM, Mispireta LA, Corso PJ, Qazi AG, et al. Coronary artery bypass without cardiopulmonary bypass. Ann Thorac Surg 1992;54:1085–92.
4. Benetti FJ, Naselli G, Wood M, Geffner L. Direct myocardial revascularization without extracorporeal circulation. Experience in 700 patients. Chest 1991;100:312–6.
5. Adams JE 3rd. Clinical application of markers of cardiac injury: basic concepts and new considerations. Clin Chim Acta 1999;284:127–34.
6. Adams JE 3rd, Abendschein DR, Jaffe AS. Biochemical markers of myocardial injury. Is MB creatine

kinase the choice for the 1990s? Circulation 1993; 88: 790–63.

7. Malik V, Kale SC, Chowdhury UK, Ramakrishnan L, Chauhan S, Kiran U. Myocardial injury in coronary artery bypass grafting: on-pump versus off-pump comparison by measuring heart-type fatty-acid-binding protein release. Texas Heart Institute Journal. 2006;33(3):321.
8. Schlattner U, Tokarska-Schlattner M, Wallimann T (February 2006). "Mitochondrial creatine kinase in human health and disease". Biochimica et Biophysica Acta 1762 (2): 164–80.
9. Domanski MJ. Prognostic implications of troponin T and creatine kinase–MB elevation after coronary artery bypass grafting. American heart journal. 2012; 164(5):636-7.
10. Costa MA, Carere RG, Lichtenstein SV, Foley DP, de Valk V, Lindenboom W, et al. Incidence, predictors, and significance of abnormal cardiac enzyme rise in patients treated with bypass surgery in the arterial revascularization therapies study (ARTS). Circulation. 2001;104(22):2689-93.
11. Brener SJ, Lytle BW, Schneider JP, Ellis SG, Topol EJ. Association between CK-MB elevation after percutaneous or surgical revascularization and three-year mortality. Journal of the American College of Cardiology. 2002;40(11):1961-7.
12. Kini A, Marmur JD, Kini S, Dangas G, Cocke TP, Wallenstein S, et al. Creatine kinase-MB elevation after coronary intervention correlates with diffuse atherosclerosis, and low-to-medium level elevation has a benign clinical courseimplications for early discharge after coronary intervention. Journal of the American College of Cardiology. 1999;34(3):663-71.
13. Ramsay J, Shernan S, Fitch J, et al. Increased creatine kinase MB level predicts postoperative mortality after cardiac surgery independent of new Q waves. J Thorac Cardiovasc Surg. 2005;129(2):300-306
14. Robinson DJ, Christenson RH. Creatine kinase and its CK-MB isoenzyme: the conventional marker for the diagnosis of acute myocardial infarction. The Journal of emergency medicine. 1999;17(1):95-104.
15. ACC/AHA guideline update on perioperative cardiovascular evaluation for noncardiac surgery: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines 2002. Available at: American College of Cardiology, www.acc.org; American Heart Association, www.americanheart.org.
16. Landesberg G, Mosseri M, Zahger D, et al. Myocardial infarction following vascular surgery: the role of prolonged, stress-induced, ST-depression-type ischemia. J Am Coll Cardiol 2001;37:1858 –63.
17. Badner NH, Knill RL, Brown JE, et al. Myocardial infarction after noncardiac surgery. Anesthesiology 1998;88:572–8



THE EFFECTS OF ADMINISTRATION OF MYO-INOSITOL ON HORMONAL PARAMETERS IN POLYCYSTIC OVARY SYNDROME (PCOS) PATIENTS

Farukh Bashir,[1] Khawar Abbas Chaudhry,[2] Mujtaba Hasan Siddiqui,[3] Asif Islam,[4] Rizwan Elahi,[5] Muhammad Azhar Shah[6]

How to cite: Bashir F, Chaudhry KA, Siddiqui MH, Islam A, Elahi R, Shah MA. The effect of administration of myo-inositol on hormonal parameters in polycystic ovary syndrome (PCOS) patients. JAIMC. 2021; 19(1): 151-156.

Abstract

Objective: To evaluate the effects of the administration of myo-inositol (MYO) in patients with polycystic ovary syndrome (PCOS), on hormonal parameters. It was a Clinical trial study conducted from January 2018 to June 2019

Methodology: One-hundred patients in the age group of 25–35 year were enrolled with PCOS, infertility and most of them were obese. Patients with pregnancy and lactation, cardiovascular diseases, kidney or Liver problems, any kind of malignancy, other diseases causing hormonal disturbances eg Cushing's disease, and on any drug intake-like anti-diabetic, estrogen and progesterone, were excluded from the study. 105 PCOS patients were enrolled finally after informed consent. All hormonal evaluations of the enrolled patients were done before and after 12 weeks of therapy (myo-inositol 2 gram plus folic acid 400µg every day. Ultrasound examinations and Ferriman-Gallwey score were also performed.

Conclusion: Our findings suggest that the addition of myo-inositol to folic acid in non PCOS-patients undergoing multiple follicular stimulation for in-vitro fertilization may reduce the numbers of mature oocytes and the dosage of rFSH whilst maintaining clinical pregnancy rate. Further, a trend in favor of increased incidence of implantation in the group pretreated with myoinositol was apparent in this study. Further investigations are warranted to clarify this pharmacological approach, and the benefit it may have for patients.

Keywords: Anovulation, myo-inositol, d-chiro-inositol, insulin resistance.

Polycystic ovary syndrome (PCOS) is a common yet often overlooked medical condition in women of childbearing age. It impacts both the reproductive system and metabolic health due to the effects of excess male hormones and insulin resistance. Menstrual irregularities, weight gain, acne, and excess hair growth are some common symptoms.

1. Farukh Bashir
2. Khawar Abbas Chaudhry
3. Mujtaba Hasan Siddiqui
4. Asif Islam
5. Rizwan Elahi
6. Muhammad Azhar Shah

1,2. Continental Medical College, Lahore
3,6: Akhtar Saeed Medical & Dental College, Lahore
4. Evercare Hospital, Lahore
5. Madina Munawwara, Saudi Arabia

Correspondence:
Dr. Farukh Bashir, *Assistant Professor and Consultant Gynaecologist Continental Medical College, Lahore.*
E-Mail: drfarrukhawan@gmail.com

Submission Date: 14-11-2020
1st Revision Date: 12-12-2020
Acceptance Date: 19-12-2020

Knowing the causes and treatment of PCOS can make it easier to live with it and prevent its long-term complications. Polycystic ovary syndrome (PCOS) is a common disease that affects 5−21% of women during their reproductive life.[1] Both the etiology and diagnosis of the syndrome are controversial. In fact, the Consensus Meeting in Rotterdam and The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004 was organized to better define and reach a consensus in the scientific community of diagnostic criteria of the syndrome.[2,3] To state the presence of PCOS, at least two of the following criteria should be present:

(i) Chronic anovulation disorder (oligo- or anovulation up to amenorrhea);

(ii) Clinical or biochemical signs of hyper-androgenism (acne or hirsutism).

(iii) Presence of micro polycystic ovaries at ultrasound or the presence of 12 or more follicles with a diameter of 2 ± 9 mm in each ovary, and/or increased ovarian volume (>10 ml).[4]

Although the Rotterdam criteria have been widely accepted, it has recently become clear that a new clinical aspect needs to be accounted – the metabolic feature of insulin resistance. An extensive literature research has demonstrated that insulin resistance is a frequent finding in PCOS patients, regardless of body mass index (BMI). Insulin resistance is a specific biological adaptation that induces a compensatory hyper insulinemia in approximately 70−80% of women with PCOS and central obesity, as well as in 15−30% of lean women diagnosed with PCOS.[5,6]

METHODOLOGY

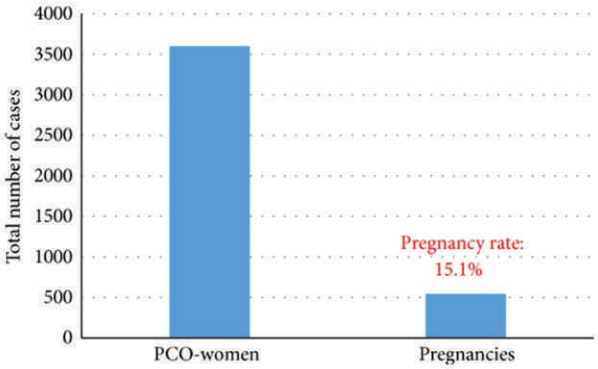
We reviewed and found out that at our center, between January 2018 and June 2019, reports were generated of 100 women with a PCOS and infertility according to the Rotterdam classification. These women were started on myoinositol and folic acid at a dosage of 2 × 2000 mg myoinositol and 2 × 200µg folic acid per day respectively and used it for at least 2-3 months. The primary outcome of the study was to determine the ovulatory function restoration and the pregnancy rate after treatment. The pregnancies were documented and registered, and these women were followed up throughout the pregnancy period. Secondary outcome was the evaluation of side effects reported in those patients undergoing treatment. In a subgroup of patients, hormonal values were also evaluated. The values investigated were testosterone, free testosterone, and progesterone. In this patient group, the pregnancy outcome has also been checked.

RESULTS

The data of 100 patients with a PCOS was evaluated. According to the obtained record 78 women experienced an improvement of their menstrual cyclicity towards ovulatory cycles. Among them, a total of 16 women became pregnant. The pregnancies occurred after the intake of two to three months of myoinositol and folic acid. This means a ratio of 16.1% of the investigated women became pregnant during this observational study. No occurrence of twin pregnancy was documented.

No relevant side effects have been reported in the patients taking myoinositol and folic acid product.

In the subgroup of 32 patients where hormonal values were evaluated, a significant improvement of androgen levels and a rise in the progesterone values were observed.



DATA COLLECTION AND ANALYSIS

Two review, we selected eligible studies, extracted data, and assessed the risk of bias. The primary outcomes were live birth and adverse effects; secondary outcomes included clinical pregnancy rates and ovulation rates. We pooled studies using a fixed-effect model, and we calculated odds ratios (ORs) with 95% confidence intervals (CIs). We assessed the overall quality of the evidence by applying GRADE criteria.

DISCUSSION

It has recently been proposed (in light of the relevant metabolic characteristics) that PCOS patients should be classified according to their metabolic features. It has been suggested that PCOS can be of two types:

i) A newer one, having higher metabolic risk, and proposed name for it 'metabolic reproductive syndrome' (MRS).

ii) A classic reproductive phenotype of PCOS.[7]

There are numerous new methods which have been proposed to manage insulin resistance, one of these is use of inositol. There are two types stereo-isomers of inositol: d-chiro-inositol (DCI) and myo-inositol (MYO). MYO is the inositol triphosphate precursor and it regulates thyroid-stimulating hormone (TSH), insulin and FSH. DCI is formed from the myo-inositol through an insulin-dependent pathway. Many early studies have shown that inositol therapy is beneficial in PCOS treatment, but no meta-analysis has been found to date. So, our aim is to review the clinical effects of use of inositol in PCOS.

Although the pathogenesis of PCOS is still controversial,[8] the presence of abnormal LH and relatively low FSH secretion changes the LH:FSH ratio (>2.5).[9] Such gonadotrophin impairment is at the basis of the elevated androgen secretion as well as of the abnormal follicular development, both due to the higher stimulation on theca cells.[10] The elevation of androgen plasma concentrations (with or without clinical signs) is a classic feature of PCOS, although not constant,[9] and it is mainly of ovarian origin with an adrenal contribution. Some of PCOS women might have a mild defect in steroidogenic in adrenal glands (like 21-hydroxylase) and some have a higher adrenal hyperactivation due to stress.[11] The androgens, androstenedione and testosterone are in fact ovarian origin, and its adrenal give basic contribution of dehydroepiandrosterone sulphate (DHEAS) elevation. An excess of circulating androgens induces a higher peripheral conversion towards the potent androgen dihydrotestosterone (DHT), and depending on the amount of such conversion and/or on the sensitivity of skin to androgens, hirsutism may easily occur.

It is well known that gonadal steroids classically bind to SHBG, being biologically inactive, and that less than 3% of testosterone circulates as unbound in the serum. However, the excess of androgens in PCOS induces a lower hepatic synthesis of SHBG or other binding proteins, which causes a relative excess of free circulating androgens, facilitating the genesis of hirsutism.[6]

An additional feature is that insulin sensitivity is affected directly and indirectly by androgens, because they may directly inhibit peripheral and hepatic insulin action. In fact, it has been demonstrated that testosterone modulates post-binding signal, reducing the number and efficiency of glucose transport proteins, such as the type 4 glucose transporter (GLUT-4), thus inducing insulin resistance in women with PCOS, especially in the most metabolically active tissues such as muscle and fat.[12] This situation is more severe in obese patients, due to abdominal fat, as they show a free androgen and insulin plasma concentration as well as insulin resistance higher than weight-matched controls.[13] In addition, obese subjects show that hepatic insulin excretion and insulin-stimulated glucose uptake in skeletal muscle is improved by free fatty acids and androgens, therefore increasing both insulin resistance and compensatory hyperinsulinemia.[14,15,16] This explains, at least in part, how in overweight or obese patients any excess of weight can further induce a reduction of peripheral tissue sensitivity to insulin, thus inducing hyperinsulinemia.[6]

This insulin resistance could occur because of abnormal plasma adiponectin and leptin concentrations. Adiponectin, an adipocyte-derived collagen-like protein, is synthesized by adipose tissue and released into the circulation.[17,18] Leptin is another adipocyte hormone encoded by the human obese (ob) gene and transmits metabolic signals to the neuronal networks in the brain so as to modulate the hypothalamic activity affecting the pituitary– ovarian axis.[19] As PCOS patients – mainly if obese – show reduced adiponectin and elevated leptin plasma concentrations, it has been demonstrated that there is a positive correlation between the serum leptin concentrations and the clinical and hormonal indices of IR.[20] In addition, leptin is linked to neuropeptide Y modulation on the reproductive axis, thus being involved in reproductive disturbance.[21]

Effect of MYO & DCI have been seen in sub

fertile females having PCOS, MYO have been shown the best results and improved egg quality, ovulation. In Gynecological Endocrinology a study was published (2007), twenty-five females who took 4g/day of MYO and for at least 6 months and during treatment 88 percent of women had one spontaneous menstrual cycle, and normal ovulation in 72% of women. A total of 10 women became pregnant pregnancies, 40%[22] in patients with PCOS Raffone et al compared the effects of metformin and MYO. 60 patients received 1,500 mg/day of metformin; other sixty ladies took 400 mcg of folic acid plus 4 g/day of MYO. Ovulation was restored in sixty five percent of patients treated with MYO compared to fifty percent in the metformin treated patients. More pregnancies occurred In the MYO patient's pregnancy rate more than patients taking metformin (18% vs. 11%).[23]

Adiponectin and leptin. Adiponectin, an adipocyte-derived collagen-like protein, is synthesized by adipose tissue and released into the circulation.[17,18] Leptin is another adipocyte hormone encoded by the human obese (ob) gene and transmits metabolic signals to the neuronal networks in the brain so as to modulate the hypothalamic activity affecting the pituitary–ovarian axis.[19] As PCOS patients – mainly if obese – show reduced adiponectin and elevated leptin plasma concentrations, it has been demonstrated that there is a positive correlation between the serum leptin concentrations and the clinical and hormonal indices of IR.[20] In Y chromosome modulation a neuropeptide leptin is needed for reproductive, this shows its role in reproductive disturbance.[21]

Both have been studied MYO and DCI effect have been observed in different studies in infertile females with PCOS, it has also been observed that MYO showed the best results in egg quality and ovulation .In Gynecological Endocrinology, a study was published in 2007 , twenty five females who received MYO (4g/day) for 6 months. As a result: Eighty eight percent of women had at least once menstrual cycle spontaneously, and in seventy two percent started normal ovulatory cycles. A total of 10 pregnancies (40% of patients) were obtained.[22]

A study published in the European Review Medical Pharmacology, in patients who are undergoing fertility treatments and having PCOS both types of inositol effects observed. One group received 2g of MYO two times a day and in another group given 6g of DCI twice a day. Women who received MYO had better, more mature eggs and more pregnancies than those who took DCI.[24]

Metabolic improvement has been observed by using MYO and DCI in PCOS, with MYO shown the best effect. In a large randomized, double-blind, placebo-controlled trial it has observed that MYO (4 g/day) for fourteen weeks, marked weight reduction, HDL good" cholesterol levels increased and also reduced leptin levels in patients with PCOS, no change in insulin levels was seen.[25]

In a double-blind placebo trial, Costantino et al showed that MYO (4 g/day) decreased insulin, triglycerides, testosterone, and blood pressure in women with PCOS.[26]

Venturella et al observed that giving 2g/day of MYO for 6 months showed marked weight reduction and improvement in HDL and LDL levels. MYO at 1,200 mg/day for 12 weeks significantly decreased androgens and insulin in non-obese women with PCOS.[27]

Myo and d-Chiro Inositol Combined, MYO has been well documented to be superior to DCI in improving insulin resistance, egg quality and reducing the risk for gestational diabetes in women with PCOS. However, when MYO is combined with DCI in an optimal ratio, the best results are seen. Every tissue in the body has its own ratio of MYO to DCI (MYO is always much higher). DCI is produced from MYO when needed. New research has shown that a combination of MYO and DCI is a more effective approach for treating PCOS. Women with PCOS who took a combination of MYO and DCI with a physiologic ratio of 40:1 (as seen in plasma), had better results than taking one supplement alone.

These positive results include reduced risk of metabolic disease in PCOS overweight patients and improved IVF outcomes, some authors suggest that "the combined administration of MYO and DCI in a ratio of 40:1, should be considered as the first line approach in PCOS."

CONCLUSION

Our findings suggest that the addition of myo-inositol to folic acid in non PCOS-patients undergoing multiple follicular stimulation for in-vitro fertilization may reduce the numbers of mature oocytes and the dosage of rFSH whilst maintaining clinical pregnancy rate. Further, a trend in favor of increased incidence of implantation in the group pretreated with myoinositol was apparent in this study. Further investigations are warranted to clarify this pharmacological approach, and the benefit it may have for patients.

Women with a PCOS and infertility according to the Rotterdam classification, started with the intake of myoinositol and folic acid at a dosage of 2×2000 mg myoinositol and 2×200 µg folic acid per day and used it for at least 2-3 months. The primary outcome of the study was to determine the ovulatory function restoration and the pregnancy rate after treatment. The pregnancies were documented by the gynecologists and registered in a database, and these women were followed up during the whole pregnancy. Secondary outcome was the evaluation of side effects reported in those patients undergoing treatment. In a subgroup of patients, hormonal values were also evaluated. The values investigated were testosterone, free testosterone, and progesterone. In this group of patients, the pregnancies outcome has also been checked.

Acknowledgement

The authors are thankful to Dr. Rizwan Elahi, Consultant Physician and Nephrologist, King Fahad National Guards Hospital, Madina Munawara, Kingdom of Saudi Arabia, for reviewing the literature and sorting out the reference articles.

REFERENCES

1. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar- Morreale HF, Futterweit W, et al. Task force on the phenotype of the polycystic ovary syndrome of the androgen excess and PCOS so
2. The androgen excess and PCOS society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009;91:456- 88.
3. Fauser B, Taratzis B, Chang J, Aziz R. ESHRE/ ASRM-Consensus document on polycystic ovary syndrome. Fertil Steril. 2004;18:19-25.
4. Genazzani AD, Prati A, Santagni S, et al. Differential insulin response to myo-inositol administration in obese polycystic ovary syndrome patients. Gynecol Endocrinol. 2012;28(12):969-973.
5. Human Molecular Genetics 3, 1873–1876. Ciampelli M, Fulghesu AM, Cucinelli F et al. 1999 Impact of insulin and body mass index on metabolic and endocrine variables in polycystic ovary syndrome. Metabolism 48, 167–172.
6. Insulin resistance is a specific biological adaptation that induces a compensatory hyperinsulinaemia in approximately 70 − 80% of women with PCOS and central obesity, as well as in 15 − 30% of lean women diagnosed with PCOS (Ciampelli et al, 1999, Fauser et al, 2012, Genazzani et al, 2010).
7. Dunaif,A;Fauser.B.C; 2013.Renaming PCOS: a two state solution.j.clin.endocrinol.metab.98,4325-4328.
8. Robert L.Rosenfield ,David A,Ehermann,Endocrine Reviews, Volume 37, Issue 5, 1 October 2016, Pages 467–520, https://doi.org/10.1210/er.2015-1104.
9. Hirschburg,A.l.2009;Polycystic ovary syndrome, obesity and reproductive imolications. Woman health 5,529-5.
10. Nelson VL et al. (2001) Augmented androgen production is a stable steroidogenic phenotype of propagated theca cells from polycystic ovaries. Mol Endocrinol 13: 946–957.
11. Genazzani, A.R., 1993. The concomitant release of androstenedione with cortisol and luteinizing hormone pulsatile releases distinguishes adrenal from ovarian hyperandrogenism. Gynecol. Endocrinol.
12. Ciaraldi, T.P., el Roeiy, A., Madar, Z., Reichart D., Olefsky J.M., Yen S.S., 2002. Cellular mechanisms of insulin resistance in polycystic ovarian syndrome. J. Clin. Endocrinol. Metab. 75, 577– 583.
13. Kirschner, M.A., Samojlik, E., Dreika, M., Szmal E., Schneider G., Ertel N., 1990. Androgen-estrogen metabolism in women with upper body versus lower

body obesity. J. Clin. Endocrinol. Metab. 70, 473–479. Kompanje, E.J.

14. Pasquali, R., Gambineri, A., 2006. Insulin-sensitizing agents in polycystic ovary syndrome. Eur. J. Endocrinol. 154, 763–775.
15. Peiris, A.N., Mueller, R.A., Struve, M.F., Smith G.A., Kissebah A.H., 1987. Relationship of androgenic activity to splanchnic insulin metabolism and peripheral glucose utilization in premenopausal women. J. Clin. Endocrinol. Metab. 64, 162–169.
16. Rebuffe-Scrive, M., Marin, P., Bjorntorp, P., 1991. Effect of testosterone on abdominal adipose tissue in men. Int. J. Obes. 15, 791– 795.
17. Stumvoll M, Tschritter O, Fritsche A, Staiger H, Renn W, Weisser M, Machicao F, Haring H. Association of the T-G polymorphism in adiponectin (exon 2) with obesity and insulin sensitivity: interaction with family history of type 2 diabetes. Diabetes 2002; 51:37–41.
18. Trujillo, M.E., Lee, M.J., Sullivan, S., Feng, J., Schneider, S.H., Greenberg, A.S., Fried, S.K., 2006. Tumor necrosis factor alpha and glucocorticoid synergistically increase leptin production in human adipose tissue: role for p38 mitogen-activated protein kinase. J. Clin. Endocrinol. Metab. 91, 1484-1490.
19. Chakrabarti, J., 2013. Serum leptin level in women with polycystic ovary syndrome: correlation with adiposity, insulin, and circulating testosterone. Ann. Med. Health Sci. Res. 3, 191–19.
20. Chen, C.I., Hsu, M.I., Lin, S.H., Chang, Y.C.I., Hsu, C.S., Tzeng, C.R., 2015. Adiponectin and leptin in overweight/obese and lean women with polycystic ovary syndrome. Gynecol. Endocrinol. 31, 264–268.
21. Jacobs, H.S., Conway, G.S., 1999. Leptin, polycystic ovaries and polycystic ovary syndrome. Hum. Reprod. Update 5, 166–171.
22. Papaleo E, Unfer V, Baillargeon JP, De Santis L, Fusi F, et al. (2007) Myo-inositol in patients with polycystic ovary syndrome: A novel method for ovulation induction. Gynecological Endocrinology 23: 700-703. Link: https://goo.gl/D8rQPv.
23. Raffone E, Rizzo P, Benedetto V. Insulin sensitiser agents alone and in co-treatment with r-FSH for ovulation induction in PCOS women. Gynecol Endocrinol. 2010;26(4):275-280.
24. Bizzarri M, Carlomagno G (2014) Inositol: History of an effective therapy for polycystic ovary syndrome. Eur Rev Med Pharmacol Sci 18: 1896-1903. Link: https://goo.gl/tpUYRt.
25. Gerli S, Papaleo E, Ferrari A, Di Renzo GC (2007) Randomized, double blind placebo-controlled trial: effects of myo-inositol on ovarian function and metabolic factors in women with PCOS. Europ rev med pharmacol sci 11: 347-354. Link: https://goo.gl/ BQsbix.
26. Costantino D, Minozzi G, Minozzi E, Guaraldi C. Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. Europ review med pharmacol sci. 2009; 13(2):105-110.
27. Venturella R, Mocciaro R, De Trana E, D'Alessandro P, Morelli M, Zullo F. [Assessment of the modification of the clinical, endocrinal and metabolical profile of patients with PCOS syndrome treated with myo-inositol]. Minerva ginecologica. 2012;64(3):239-243

FREQUENCY OF PANIC DISORDERS AND SOCIAL PHOBIA IN TEENAGE PREGNANCY PRESENTING IN A TERTIARY HOSPITAL IN PAKISTAN

Muhammad Tariq,[1] Shahnaz Fatima,[2] Nadeem Akhtar,[3]
Saqib Maraj Aslam Bajwa,[4] Shafqat Huma,[5] Muhammad Nauman Shad[6]

How to cite: Tariq M, Fatima S, Akhtar N, Bajwa SMA, Huma S, Shad MN. Frequency of panic disorders and social phobia in teenage pregnancy presenting in a tertiary hospital in Pakistan. JAIMC. 2021; 19(1): 157-160.

Abstract

Background: Teenage pregnancy is a high risk pregnancy. It is associated with a wide range of subsequent adverse health and social outcomes i.e. anxiety disorders (social phobia and panic disorders).

Objective: The objective of the study was to determine the frequency of panic disorders and social phobia in teenage pregnancies presenting in the antenatal clinic of a tertiary hospital in Lahore

Methodology: This was a cross-sectional study carried out in six months, involving 150 pregnant teenagers in the 13-19 years range. Each subject was interviewed in a comfortable setting ensuring privacy and confidentiality and assessed for panic disorders & social phobia, according to ICD-10 criteria.

Results: Frequency of social phobia in patients with teenage pregnancy was evaluated which was found to be 14% (n=129), while the frequency of panic disorder in patients with teenage pregnancy was recorded in 15.33% (n=23).

Conclusion: The frequency of anxiety disorders (social phobia and panic disorders) is high among patients with teenage pregnancy. So, it is recommended that every patient who presents with teenage pregnancy should be sorted out for anxiety disorders. However, it is also required that every setup should have their surveillance in order to know the frequency of the problem.

Key Words: Teenage pregnancy, anxiety disorders, social phobia, panic disorders

Teenage pregnancy is defined as pregnancy in women in their teen years (under age 20).[1] Every year girls less than 20 years of age give birth to13 million newborns. In developing countries, more than one third of women give birth before the age of 20.[2]

1. Muhammad Tariq
2. Shahnaz Fatima
3. Nadeem Akhtar
4. Saqib Maraj Aslam Bajwa
5. Shafqat Huma
6. Muhammad Nauman Shad

1. Department of Psychiatry, Sahara Medical College, Narowal
2,6. Sahara Medical College, Narowal
3. Psychiatry Department, Services Institute of Medical Sciences, Lahore
4. Gujranwala Medical College, Gujranwala
5. Psychiatry Department, College of Medicine and Dentistry University of Lahore, Lahore

Correspondence:
Dr. Muhammad Tariq, Assistant Professor, *Department of Psychiatry, Sahara Medical College, Narowal. Email: dr.muhdtariq@gmail.com*

Submission Date: 07-10-2020
1st Revision Date: 11-11-2020
Acceptance Date: 16-11-2020

Pregnancy during teen years has become an important public health problem throughout the world because of the poor social support such teen-agers get. Leading causes of death for girls under 20 in poorer countries include complications from these early pregnancies and childbirths including infant mortality.[3]

In recent years, there has been extensive study of the relationship between motherhood and psychiatric disease. Depressive symptoms are experienced by 10 to 27 % of women in pregnancy; major depressive disorder is experienced by 2-11 % [4]. One factor that makes teenage pregnancies and childbirths very dan-gerous in many developing countries is the social pressure to reproduce as early as possible.

Social phobia diagnostically is defined by persistent fear of social or performance situations

that may involve scrutiny and other people's disapproval. Exposure to a feared situation causes marked distress, attacks of panic, or avoiding people. Panic disorder is defined by discrete episodes of marked autonomic arousal (e.g. increase in heart rate) according to DSM IV criteria. Catastrophic thinking (e.g. fear of fainting, losing control) accompany these symptoms. Substance abuse or medical conditions are not a direct cause of all these symptoms.[5]

During teenage pregnancy, the incidence of panic disorder is unknown. In some retrospective studies pregnancy protects against panic attacks. Changes in PCO_2 during pregnancy reduce anxiety's physiological trigger as theorized in one study.[6]

A recent prospective study, on the other hand, failed to support these findings and shows that the course of the pregnancy disorder is predicted by the intensity of the disorder before pregnancy. 260 pregnant women with panic disorder in the study showed that 30 percent of them experienced an improvement in symptoms, while 19 percent worsened.

Generalized social anxiety disorder is mostly characterized by significant avoidance, with harmful consequences on social relationships, leading to lower achievements in educational institutes and in the workplace. Besides quality of life declines, there is increase of suicide rate as high as 22%. [8]

Very few studies in Pakistan have been conducted on anxiety disorders in teenage pregnancies, so this study was conducted to determine the frequency of social phobia and panic disorder in teenage pregnancies in the country.

METHODOLOGY

This was a cross-sectional study was conducted at antenatal Clinic of Obstet-rics & Gynecology, Services Hospital, Lahore. Duration of study was six months. 150 pregnant teenagers were included in the study.

Inclusion Criteria:

- Teen age pregnancies (as per operational definition)
- Age 13-19 years

Exclusion Criteria:

- Psychiatric disorder other than anxiety disorders like depression, schizophrenia bipolar affective disorder etc. (from history, mental state, examination and previous record)
- Women with any other chronic medical disorders e.g. hypertension, diabetes mellitus and ischemic Heart Disease (IHD) on history and diagnoses by physician.

A proforma was used to collect data from outdoor patients visiting Obstetrics and Gynecology department. A written consent was taken from all patients to include their data in the research work. Each subject was interviewed in a comfortable setting ensuring privacy and confidentiality and assessed for panic disorder and social phobia. The diagnostic criteria of social phobia and panic disorder were according to international classification of disease 10th revision (ICD-10).[9]

RESULTS

Age distribution of the subjects was done. Age range was 13-19 years; majority of the patients were 19 years of age i.e. 44.66 % (n=67). 34.67 % (n=52) were between 16-18 years and 20.67 % (n=31) were between 13-15 years of age. Mean and standard deviation was calculated as 16.23±2.67. (Table No.1)

Frequency of social phobia in patients with teenage pregnancy was evaluated which was found in 14 % (n=21) of patients, while 86 % (n=129) had no findings of social phobia.

Frequency of panic disorder in patients with teenage pregnancy was recorded in 15.33 % (n=23) of subjects, while 84.67 % (n=127) had no findings of panic disorder. (Table No. 2)

Table 1: *Age Distribution of the Subjects*

Age (in years)	No. of Cases	Percentage
13-15	31	20.67
16-18	52	34.67
19	67	44.66
Total	**150**	**100**
Mean and S.D.	**16.23 ± 2.67**	

DISCUSSION

Teenage pregnancy is a high risk pregnancy. The worldwide incidence of adverse obstetrical outcome is higher among teenage mothers. Although teenage pregnancy can be a positive experience, particularly in the later teenage years[10,11] it is associated with a wide range of subsequent adverse health and social outcomes.[12,13] These associations remain after adjusting for pre-existing social, economic, and health problems.[14]

Table 2: Frequency of Social Phobia & Panic Disorder in Patients with Teenage Pregnancy (n=150)

Social phobia	No. of cases	Percentage
Yes	21	14
No	129	86
Total	150	100
Panic disorder	**No. of cases**	**Percentage**
Yes	23	15.33
No	127	84.67
Total	**150**	**100**

Despite being a positive experience especially in the later teenage years,[10,11] teenage pregnancy is associated with a wide range of adverse health and social outcomes.[12,13] After adapting to pre-existing social, economic and health problems, these associations still remain.[14]

Very few studies in Pakistan have been carried out on anxiety disorders in teenage pregnancies, so this study was planned to determine the frequency of anxiety disorders in teenage pregnancies. The results of the study recommend screening of panic disorders and social phobia in teenage pregnancies in the antenatal clinics and referral to psychiatry department for early management, because it may lead to adverse perinatal out comes as well.

The findings of our study are in agreement with the study by Balaha MH who found panic disorders and social phobia in (10.34%) in patients with teenage pregnancy.[1] As suggested by some authors, physical and mental health issues that teenage mothers report are very much linked with the social and economic drawbacks that they face.

In a study comparing pregnant teenagers with a peer group who were sexually active but not pregnant and a peer group who were not sexually active, the pregnant teenagers did not differ from the others in physical health. Higher rates of mental health problems and symptoms of conduct disorders were seen in the pregnant teenagers, together with the sexually active group.[15]

In view of the above discussion, it may be determined that anxiety disorders (social phobia and panic disorders) are prevalent in teenage pregnancy; though these are not having great incidence but they cannot be neglected. Furthermore, this study is showing the primary data in Pakistan regarding anxiety disorders and it may be helpful for referral of these patients to psychiatry department for early management, because it may lead to adverse perinatal out comes as well.

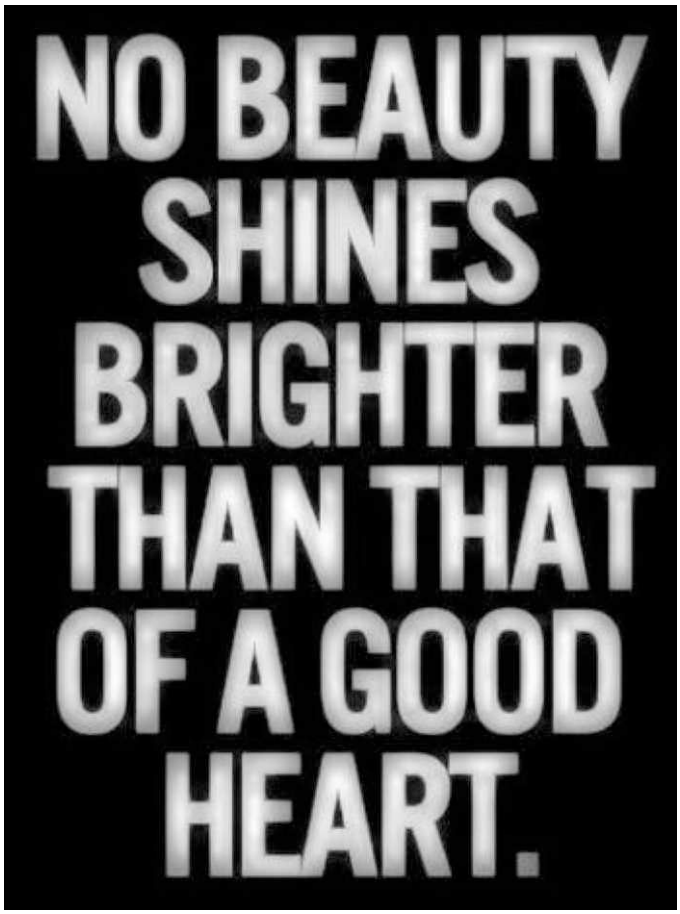
CONCLUSION

The frequency of anxiety disorders (social phobia and panic disorders) is high among patients with teenage. So, it is recommended that every patient who presents with teenage pregnancy should be sorted out for anxiety disorders. However, it is also required that every setup should have their surveillance in order to know the frequency of the problem.

REFERENCES

1. Balaha MH, Amr MA, El-Gilany AA, Al-Sheikh FM. Obstetric and Psychiatric Outcomes in a Sample of Saudi Teen-Aged Mothers. TAF Prev Med Bull 2009; 8:285-90.
2. States of the Worlds Mothers. Children having children. Where young mothers are most at risk. 2004; pp. 8-26.
3. Yadav S, Choudhary D, Narayan KC, Mandal RK, Sharma A, Chauhan SS, Agrawal P. Adverse Reproductive Outcomes Associated With Teenage Pregnancy. Mcgill J Med 2008; 11:141–4.
4. Hamid F, Asif A, Haider II. Study of anxiety and depression during pregnancy. Pak J Med Sci 2008; 24:861-64.
5. Kessler RC, Chiu WT, Jin R. The epidemiology of panic attacks, panic disorder, and agoraphobia in the National Co morbidity Survey Replication. Arch Gen Psychiatry 2006;6 3:415–24.

6. Klein D, Skrobala A, Garfinkel R. Preliminary look at the effects of pregnancy on the course of panic disorder. Anxiety 1994/1995; 1:227–32.
7. Hertzberg T, Wahl beck K. The impact of pregnancy and puerperium on panic disorder: a review. J Psychosom Obstet Gynecol 1999; 20:59–64
8. Katzelnick DJ, Kobak KA, DeLeire T. Impact of generalized social anxiety disorder in managed care. Am J Psychiatry 2001; 158: 1999–2007.
9. ICD-10 International Classification of Diseases Tenth Revision https://icd.who.int/browse10/2010/en
10. Hoffman SD. Teenage childbearing is not so bad after all—is it? A review of new literature. Int Fam Plan Perspect 1998; 30:236-9.
11. Bonell CP. Why is teenage pregnancy conceptualized as a social problem? A review of quantitative research from the USA and UK. Cult Health Sex 2004; 6:1-18.
12. Ermisch J. Does a 'teen-birth' have longer-term impacts on the mother? Suggestive evidence from the British household panel survey. Institute for Social and Economic Research, 2003.
13. Pevalin DJ. Outcomes in childhood and adulthood by mother's age: evidence from the 1970 British cohort study. Institute for Social and Economic Research, 2003.
14. Barrington A, Diamond I, Ingham R, Stevenson J, Borgoni R, Hernandez I. Consequences of teenage parenthood: pathways which minimize the long term negative impacts of teenage childbearing: final report. University of Southampton, 2005.
15. Stiff man AR, Earls F, Robins LN. Adolescent sexual activity and pregnancy: socio-environmental prob-



EVALUATION OF TYPES AND SEVERITY OF ANEMIA IN PATIENTS PRESENTING TO ANEMIA CLINIC IN TERTIARY CARE HOSPITAL, LAHORE

Shizra Kaleemi,[1] Rabia Ahmad,[2] Fauzia Aamir[3]

How to cite: Kaleemi S, Ahmad R, Aamir F. Evaluation of types and severity of anemia in patients presenting to anemia clinic in tertiary care hospital, Lahore. JAIMC. 2021; 19(1): 161-166.

Abstract

Background: Anemia is one of the commonest medical conditions that affect different age groups including children, adults and older population. Anemia is defined as insufficient capacity of blood to carry oxygen to body to meet the physiological requirements according to age and gender. Iron deficiency is the most common cause of anemia worldwide and it affects about 2 billion people throughout the world.

Methodology: To determine the frequency of types and severity of anemia in patients presenting in Anemia Clinic of a Tertiary care Hospital, Lahore. It was a cross-sectional study conducted at Anemia Clinic, Department of Hematology, Allama Iqbal Medical College/Jinnah hospital, Lahore, from 1st June2018 to 30th November 2018.

Results: Out of 150 patients with anemia, 54% (n=81) were children (age: less than14 years). Anemia was slightly more common in females 52.6% (n=79) as compared to males 47.3% (n=71). Mean hemoglobin level was 8.0 5 ± 1.9 g/dl. Weighted prevalence for mild, moderate and severe anemia were 13.3% (n=20), 42% (n=63) and 44% (n= 67) respectively. The prevalence of microcytic anemia was very high 79.3% (n=119) as compared to normocytic 14.6% (n=22) and macrocytic anemia 6.0% (n=9).

Conclusion: Prevalence of anemia was very high in patients presenting to Tertiary Care Hospital in Lahore. The frequency of anemia was much higher in children (< 14 years) irrespective of gender. Severe anemia was more common in all age groups than mild and moderate anemia. Microcytic anemia was far more prevalent in all age groups.

Key Words: Anemia, hemoglobin, microcytic, normocytic, macrocytic

Anemia is defined as "a condition in which the number of red blood cells or their oxygen carrying capacity is insufficient to meet physiological needs, which vary by age, sex, altitude, smoking and pregnancy status."[1] Anemia is a major problem worldwide, affecting about 1.62 billion people globally.[2] Although, anemia may be due to multiple factors, but most studies confirmed that 80% cases of anemia, are due to iron deficiency.[3] Iron deficiency in children causes impaired cognitive development and behavioral abnormalities. Iron deficiency also impairs cell mediated immunity in children, resulting in reduced immunity against pathogens and increased rates of morbidity due to acute infections. Iron deficiency anemia also has a negative impact on linear growth and physical work capacity.

Iron deficiency anemia is also very common in females of reproductive age. In pregnancy, there is an increase in iron demand. WHO reports that in developing countries, 35-67%(average 56%) of pregnant females and 18% of females in industrialized countries are anemic. Anemia in pregnancy has many adverse effects on fetus like preterm birth, low birth weight, rise in perinatal mortality as well as increases maternal morbidity and mortality.

1. Shizra Kaleemi 2. Rabia Ahmad
3. Fauzia Aamir
1. *Akhtar Saeed Medical and Dental College, Lahore*
2. *Hematology Department, Allama Iqbal Medical College, Lahore*
3. *Services Hospital / SIMS*

Correspondence:
Dr. Shizra Kaleemi, *Akhtar Saeed Medical and Dental College, Lahore*

Submission Date: 02-10-2020
1st Revision Date: 19-11-2020
Acceptance Date: 22-11-2020

Other causes of anemia include vitamin B12, folate and vitamin A deficiencies, parasitic infection, chronic inflammation, blood loss, hemolytic anemia, hemoglobinopathy and aplastic anemia. Anemia causes weakness, easy fatigue, loss of energy, difficulty to concentrate, breathlessness, dizziness and insomnia. When a significant proportion of a population is anemic, it can influence the gross productivity of that population[4].

The rationale of this study is to determine the types of anemia and its grades of severity in patients as anemia is widely prevalent in developing countries and according to World Health Organization (WHO) estimates; two billion of world's population is anemic and it is associated with several complications. This study will not only highlight the types and severity of anemia in our setting but also will help us in recommending guidelines for management and treatment of this treatable disease.

METHODOLOGY

- It was a Cross-sectional study which included 150 patients who presented at Anemia Clinic, Department of Hematology, Allama Iqbal Medical College/Jinnah hospital, Lahore in a period of six months i.e. from 1st June to 30th November 2018. The patients with anemia (as per operational definition) of either gender and age from 6 months to 60 years were included. Hemoglobin concentration in males (>14 years) less than 13g/dl and females (>14 years) less than 12g/dl, in children (6 to 59months) hemoglobin concentration less than 11g/dl and children (5 to 14 years) less than 11.5g/dl were considered as anemia.

Pregnant females, patients with history of major surgery or with history of blood transfusion within 1 month were excluded. Informed consent was obtained from every case. Demographic data like age, sex and address were noted on the specially designed proforma. Blood samples from each case was taken for Complete Blood count(CBC) and peripheral smear in EDTA vial.. Hemoglobin (Hb), Hematocrit (Hct), RBC count and Red cell indices were determined by using Hematology Analyzer: Sysmex KX-21. Peripheral smears were analyzed for microcytic, normocytic and macrocytic picture of red blood cells (RBCs). Types of anemia were categorized as microcytic (Mean cell volume (MCV) ≤ 76fl), Normocytic (MCV 77-90fl) and macrocytic (MCV >90fl). Severity of anemia was labeled as given in table 1.

Data was collected and analyzed by using Statistical Package for Social Sciences v20.0 (SPSS). Mean and standard deviation (SD) were calculated for quantitative variables like age. Frequency and percentages were calculated for gender, types and severity of anemia. Data was stratified for age and gender. Post-stratification chi-square test was used taking p-value ≤0.05 as significant.

Table 1: *Hemoglobin Concentration(g/dl) for Assessment of Severity of Anemia*

Age	Mild Anemia	Moderate Anemia	Severe Anemia
Children (6-59months)	10-10.9	7-9.9	<7
Children (5-14 years)	11-11.4	8-10.9	<8
Male (>14 years)	11-12.9	8-10.9	<8
Female (>14 years)	11-11.9	8-10.9	<8

RESULTS

The mean hemoglobin was 8.05 ± 1.9 gm/dl ranging from 4.2-11.6 g/dl. The mean for RBC count was 4.04 ± 0.74 × 106/µl, hematocrit (Hct) 32.4 ± 5.4%, MCV 68.2 ± 11.2 fl and MCH 20.2 ± 5.2 pg. Age distribution of anemia is shown in figure:1 Maximum prevalence of anemia was seen in children (<14 years). Anemia was slightly more prevalent in females than males with M:F ratio of 0.8:1.

In this study, the most common grade of anemia was severe followed by moderate degree of anemia. Mild degree of anemia was present in only 13.3% of cases. Distribution of study subjects as per grades of severity of anemia is shown in figure.[2]

Comparison of the grades of severity between different age groups showed that severe and moderate degree of anemia was more pronounced in all age groups as compared to mild degree of anemia

(Table:2). Degree of anemia in different age groups shows statistically significant difference with p-value=0.05 (Table:2).

Among those, severe anemia was slightly more common in males (45%, n = 32) as compared to females (44%, n=35). Moderate anemia was slightly more prevalent in females 43% (n=34) as compared to 40% (n=29) in males shown in table 10. While prevalence of mild anemia was same in both genders (14%, n=10). But this difference in severity among both genders is not statistically significant as p value was 0.9 (Table:3)

Distribution of study subjects as per type of anemia is shown in Figure.3. The most common type of anemia found in this study was microcytic type of anemia. Comparison of different types of anemia in different age groups (Table:4) showed that maximum prevalence of microcytic anemia was seen in children (< 14 years).In patients in age group (14-27 years) and (28-40), microcytic anemia was more prevalent followed by normocytic anemia In patients with age 41 years and above, microcytic anemia as well as macrocytic anemia was common. Difference of type of anemia between different age groups is statistically significant (p value=0.001). There was no significant difference of prevalence of different types of anemia between both genders (p value= 0.870) shown in Table:5.

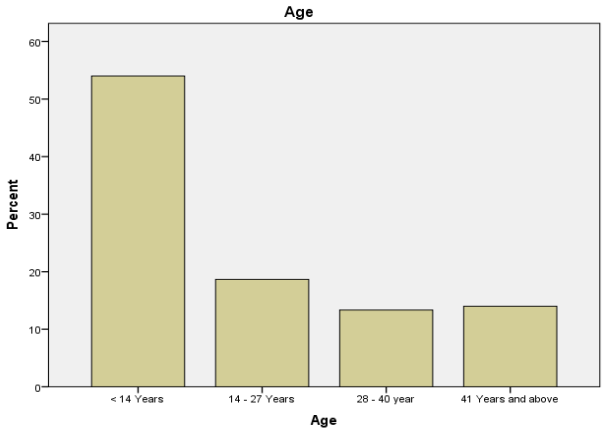


Figure 1: *Age Distribution of Anemia*

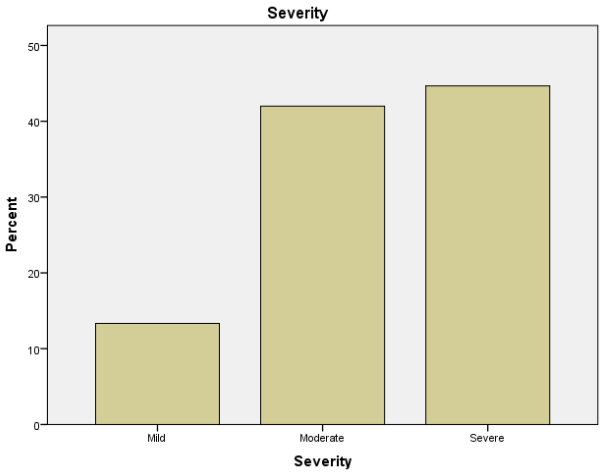


Figure 2: *Severity of Anemia*

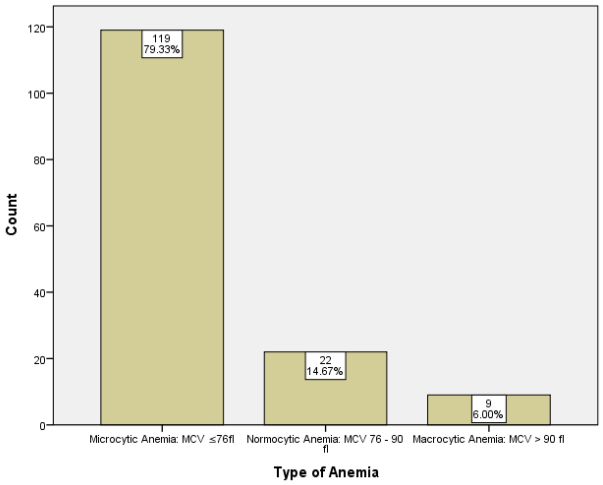


Figure 3: *Types of Anemia*

Table 2: *Age * Severity of Anemia*

Age	Severity of Anemia			Total	Chi-square P value
	Mild	Moderate	Severe		
< 14 Years	4 20.0%	38 60.3%	39 58.2%	81 54.0%	X^2 =12.506[a] P =.052
14 - 27 Years	5 25.0%	10 15.9%	13 19.4%	28 18.7%	
28 - 40 year	6 30.0%	7 11.1%	7 10.4%	20 13.3%	
41 Years and above	5 25.0%	8 12.7%	8 11.9%	21 14.0%	
Total	20 100.0%	63 100.0%	67 100.0%	150 100.0%	

Table 3: *Gender * severity of Anemia*

Gender	Severity of Anemia			Total	Chi-square P value
	Mild	Moderate	Severe		
Male	10	29	32	71	X^2 =..105[a] P =.949
	50.0%	46.0%	47.8%	47.3%	
Female	10	34	35	79	
	50.0%	54.0%	52.2%	52.7%	
Total	20	63	67	150	
	100.0%	100.0%	100.0%	100.0%	

Table 4: *Age * Type of Anemia*

Age	Type of Anemia			Total	Chi-square P value
	Microcytic Anemia: MCV ⩽ 76fl	Normocytic Anemia: MCV 76-90 fl	Macrocytic Anemia: MCV > 90 fl		
< 14 Years	79	1	1	81	X^2 = 66.796 P =.001
	66.4%	4.5%	11.1%	54.0%	
14 - 27 Years	16	12	0	28	
	13.4%	54.5%	0.0%	18.7%	
28 - 40 year	14	5	1	20	
	11.8%	22.7%	11.1%	13.3%	
41 Years and above	10	4	7	21	
	8.4%	18.2%	77.8%	14.0%	
Total	119	22	9	150	
	100.0%	100.0%	100.0%	100.0%	

Table 5: *Gender * Type of Anemia*

Gender	Type of Anemia			Total	Chi-square P value
	Microcytic Anemia: MCV ⩽ 76fl	Normocytic Anemia: MCV 76 - 90 fl	Macrocytic Anemia: MCV > 90 fl		
Male	56	10	5	71	X^2 =.279[a] P =.870
	47.1%	45.5%	55.6%	47.3%	
Female	63	12	4	79	
	52.9%	54.5%	44.4%	52.7%	
Total	119	22	9	150	
	100.0%	100.0%	100.0%	100.0%	

DISCUSSION

Anemia is very prevalent around the globe affecting millions of people especially in developing countries like Pakistan. In Pakistan, there are many factors that contribute to a huge burden of anemia like poverty, illiteracy, lack of provision of adequate health facilities especially in rural areas and discrimination of gender. This study showed that anemia is very prevalent in OPD patients presenting to Anemia Clinic, Department of Hematology, Allama Iqbal Medical College/Jinnah hospital, Lahore.

150 patients of age (6 months to 60 years) were included in this study. Among those, anemia was slightly more prevalent in females 52.6% (n=79) as compared to 47.3% (n = 71) in males. In a study conducted in a tertiary care hospital in Peshawar, Pakistan, 67.4% of male and 64.5% of female patients were found anemic.[5] Moderate anemia was more frequent in females 18.9% as compared to males 16.5% while mild and severe anemia were more common in males as compared to females.[5] While in the present study, mild and severe anemia was slightly more common in males while moderate anemia was more common in females women. In another study at Kohat, Pakistan showed similar results that moderate and severe anemia was more prevalent in females.[6]

In the present study, the prevalence of microcytic anemia was 79.3% (n = 119), normocytic anemia 14.7% and macrocytic anemia 6.0% (n=9) of patients. Iron deficiency is the major cause of microcytic hypochromic anemia. In another study performed in Bahawalpur, Pakistan showed similar results as 80% of patients have iron deficiency anemia and 20% have with non-iron deficiency anemia.[7] Another study by Habib M A et al reported that the prevalence of iron deficiency anemia in non-pregnant women of reproductive age (15-49 years) was 18.1%.[8]

In the present study, 54% of anemic patients were children(less than 14 years). Harding et al reported that in Pakistan, anemia is very common in children if they are stunted or born to already anemic mother.[9] This study also showed that the prevalence of anemia is very higher in women from low socio-economic status and who are undernourished.[9] A study showed that 74% of children less than 12 years of age living in rural areas of Punjab, Pakistan were found anemic.[10]

Another study conducted on pediatric age groups reported that out of 422 patients with microcytic hypochromic anemia, 400 were having iron deficiency anemia.[11] Iron deficiency anemia was

more common in the age group 1-6 years.[11] Ghosh A et al reported that many patients belong to lower socioeconomic status (58.5%) and a majority of patients presented with acute infections (58.5%) and rest of them with chronic infections (25.8%) and chronic non-infectious diseases (10.8%).[11] Ahmed et al reported that iron deficiency is very common in school going children without anemia.[12] Many children have iron deficiency with low ferritin levels but normal hemoglobin.[12]

Nageen et al showed in a study that 51.4% of healthy adult males were having anemia.[4] Prevalence of normocytic (47.8%) and microcytic anemia (41.1%) was high as compared to macrocytic anemia (11%).[4] While In the present study, the prevalence of microcytic anemia was high, 78.8% of males were having microcytic anemia while the prevalence of normocytic and macrocytic anemia males were 14% and 7%, respectively.

In the present study, the prevalence of macrocytic anemia was low. But Soofi et al showed in Pakistan, 52.4% and 50.8% of women are deficient of Vitamin B12 and folate respectively while the prevalence of anemia in women of reproductive age was 50.4%.[13] Females that are living in rural areas of Pakistan were less likely to develop vitamin B12 deficiency as compared to those living in urban areas.[69] It is also reported that females from Khyber Pakhtunkhwa and Kashmir are more likely to develop Vitamin B12 deficiency and are less likely to develop Folate deficiency as compared to other provinces of the country.[13] Women with daily or weekly intake of eggs are less likely to develop folate deficiency as compared to those with monthly intake of eggs.[13]

In the present study, the overall prevalence of macrocytic anemia was 6% which was comparable to 20% in another study.[14] it is seen in many studies that macrocytic anemia was more common in males.[14,15] Agarwal et al also reported that 55% of patients with macrocytic anemia were cobalmin deficient, 8% were folate deficient and results of rest were unknown.[14] So it is very important to include Vitamin B12 supplementation along with iron and folate.Pandya et al showed that a higher incidence of B12 deficiency (80%) was in patients aged 40 years and above as in the present study 77.8% were above 40 years of age.[15] The most common symptoms were weakness, fatigue, weight loss, and abnormal bowel habits.[15]

CONCLUSION

Anemia is very prevalent in patients presenting to tertiary care hospital, Lahore. Frequency of anemia was very higher among children. Iron deficiency anemia is very common along with cobalamin and folate deficiency. Large scale research is needed to measure prevalence of anemia in our population more precisely. Policies at the national level should be made to address this problem. Efforts should be made to provide proper nutritional diet, good sanitation, adequate health, and educational facilities to overcome this burden of anemia especially in school going children.

REFERENCES

1. World Health Organization. Health topics: Anemia. [cited 6 September 2017] Available from: http://www.who.int/topics/anemia/en/
2. Lam P. Anemia: causes, symptoms and treatments. [updated 23 February 2017;cited 6 September 2017] Available from: http://www.medicalnewstoday.com/articles/158800.php.
3. Hashim N, Farooqi M, Naqvi S, Jaffery HF. Anemia; moderate to severe during pregnancy. Professional Med J. 2014;21(2):247-52
4. Nageen A, Kidwai SS, Bashir F, Ara J, Munir SM. Anemia-an unnoticed entity in Asian males, a focus on the anemic parameters of adult males in Pakistan. Br J Med Med Res. 2017;22(1):1-7.
5. Shahab F, Sikandar S, Shahab A, Raziq F. Frequency of anemia in patients presenting to tertiary care hospital in Peshawar, Pakistan. Khyber Med Univ J. 2015;7(1):30-3.
6. SAJID M, Hayat U, Ashraf M, Akram M, Munir A. Frequency of Anemia in Patients Presenting to Tertiary Health Care Hospital in Kohat, Pakistan. P J M H S. 2016;10(4):130-132.
7. Malik S, Malik M, Malik S Iron deficiency anemia in bahawalpur region of pakistan: a descriptive

study: P J M H S: JAN-MAR 2016; Vol. 10,(no.1): 89-91.

8. Habib M, Greenow C, Soofi S, Ali N, Nausheen S, Ahmed I et al. Prevalence and determinants of iron deficiency anemia among non-pregnant women of reproductive age in Pakistan. Asia Pacific Journal of Clinical Nutrition. 2018;27(1):195-203.
9. Harding K, Aguayo V, Namirembe G, Webb P. Determinants of anemia among women and children in Nepal and Pakistan: An analysis of recent national survey data. Maternal & Child Nutrition. 2017; 14: e12478.
10. Sharif S, Naz S, Iram R, Manzoor F, Farasat T, Saqib M. Prevalence of Anaemia in Children of Rural Areas of Punjab. BIOLOGIA. 2017;63(2):211-215.
11. Ghosh A, Ghartimagar D, Thapa S, Sathian B, and De A. Microcytic Hypochromic Anemia in Pediatric Age Group: A Hospital Based Study in Nepal. Am J Public Health. 2015;3(4A):57-61.
12. Ahmad M, Farooq H, Maham S, Qayyum Z, Waheed A, Nasir W. Frequency of Anemia and Iron Deficiency among Children Starting First Year of School Life and Their Association with Weight and Height. Anemia. 2018;2018:1-5.
13. Soofi S, Khan G, Sadiq K, Ariff S, Habib A, Kureishy S et al. Prevalence and possible factors associated with anaemia, and vitamin B12 and folate deficiencies in women of reproductive age in Pakistan: analysis of national-level secondary survey data. BMJ Open. 2017;7(12):e018007.
14. Agarwal L, Ramawat J, Agrawala M, Rai N. A study on prevalence and causative factors of megaloblastic anaemia in Hadoti region. Annals of Applied Bio-Sciences. 2017;4(1):A31-A34.
15. Pandya H, Patel A. Clinical profile and response in patients with megaloblastic anemia. International Journal of Medical Science and Public Health. 2016; 5(2):304.

DIAGNOSTIC OUTCOME OF BONE MARROW ASPIRATION AND BIOPSY, IN A TERTIARY CARE HOSPITAL, LAHORE

Shizra Kaleemi,[1] Rabia Ahmad,[2] Fauzia Aamir[3]

How to cite: Kaleemi S, Ahmad R, Aamir F. Disgnostic outcome of bone marrow aspiration and biopsy, in a tertiary care hospital, Lahore. JAIMC. 2021; 19(1): 167-172.

Abstract

Background: Bone Marrow is involved in many hematological and non-hematological disorders. Bone marrow examination is a simple and relatively safe procedure to diagnose both benign and malignant disorders involving bone marrow.

Objective: To evaluate the spectrum of various benign and malignant disorders diagnosed by Bone Marrow aspiration and biopsy.

Methodology: The study was performed in the Hematology department, Allama Iqbal medical College/ Jinnah Hospital, Lahore, for the period of 1 year from January 2017 to December 2017. Bone marrow aspiration and trephine biopsy was performed in patients with referral from outdoors and indoors of Jinnah hospital, Lahore after complete screening.

Results: In present study, 651 patients were included during a period of 1 year. Among 651cases, malignant cases (74.2%) were more commonly seen as compared to benign cases (15.3%). Aplastic anemia was the most common benign disorder and leukemias were commonest among malignant lesions observed.

Conclusion: Bone marrow examination is an important tool to diagnose various benign and malignant disorders involving bone marrow.

Keywords: bone marrow, benign, malignant, Aplastic anemia, leukemia

Bone Marrow is involved in many hematological and non-hematological disorders.[1] Bone marrow(BM) examination is an important tool to diagnose these disorders when all the others tests are not helpful.[2] BM examination is not only diagnostically useful but also has its own prognostic value.[3] Hematological disorders include leukemias, lymphomas, aplastic anemia, myelodysplasia and myeloproliferative neoplasms while in non-hematological disorders, parasitic infections, granulomatous diseases and metastatic tumors commonly infiltrate the bone marrow.

BM examination involves 2 components: BM aspiration and trephine biopsy. In BM aspirate examination, we can appreciate numerical and cytological features of bone marrow cells. It is also useful for other diagnostic techniques like cytogenetics, molecular and flowcytometric analysis for confirmation of diagnosis. Trephine biopsy provides valuable information about Bone marrow architecture, cellularity and pattern of infiltration and fibrosis.[2,4] in a study by Gilotra et al described that 87% of cases were cases were confirmed by bone marrow aspiration and biopsy.[2]

It is a simple and relatively safe procedure that can be performed on outdoor basis under local anesthesia. It is an invasive procedure but can be performed in severe thrombocytopenia with no or little bleeding risk.[4] There are numerous indications for BM examination, most commonly being leukemia, cytopenias, staging of lymphoma and pyrexia of unknown origin.

The rationale of this study is to understand the spectrum of different indications of bone marrow examination in our population and relevant benefit

1. Shizra Kaleemi 2. Rabia Ahmad
3. Fauzia Aamir
1. Akhtar Saeed Medical and Dental College, Lahore
2. Hematology Department, Allama Iqbal Medical College, Lahore
3. Services Hospital/ SIMS Lahore

Correspondence:
Dr. Shizra Kaleemi, *Akhtar Saeed Medical and Dental College, Lahore*

Submission Date: 08-11-2020
1st Revision Date: 18-12-2020
Acceptance Date: 20-12-2020

in selecting different treatment options. The objective of this study is to evaluate the pattern of various benign and malignant lesions diagnosed by Bone Marrow aspiration and biopsy.

METHODOLOGY

The study was performed in the hematology department, Allama Iqbal medical College/ Jinnah Hospital, Lahore, for the period of 1 year from January 2017to December 2017. Non-probability sampling technique (consecutive type) was used. Patients referred for Bone Marrow examination from indoors and outdoors of Jinnah hospital, Lahore were included. Both male and female patients belonging to different age groups were included in the study. Bone marrow aspiration and trephine biopsy was performed in patients after complete clinical assessment. Written informed consent was taken from every patient. The procedure was done under aseptic conditions using local anesthesia. The most common site was posterior superior iliac spine while in infants, aspirate was taken from tibia. The slides were stained using Geimsa stain and special stains like Sudan Black B, Periodic acid Schiff (PAS) and Persian blue were also used as per need. Data was evaluated for parameters like age, gender and diagnosis of BM aspiration and biopsy using Statistical Package for the Social Sciences (SPSS) v20.0.

RESULTS

In our study, we included 651 patients who presented to Hematology Department, Allama Iqbal Medical College, Lahore from a period of 1 year from January to December 2017. The median age was 38 years with a range from 4 months to 85 years with a male to female ratio of 1.6:1. Spectrum of various disorders is shown in chart 1.

Among benign cases, aplastic anemia was found most common 47.5% (n=48), followed by Immune Thrombocytopenia (ITP) 15.3% (n=21). There were 13 cases of megaloblastic anemia and 7 cases of double deficiency anemia. Granulomas were found in trephine biopsies of 3 patients. Pure red cell aplasia was diagnosed in a patient. We had also diagnosed a patient with Gaucher's disease. Frequencies of benign cases are shown in Table 1.

Chronic Myeloid leukemia (CML) was most commonly found in malignant cases 30.6% (n=148). Among CML cases, most patients presented in chronic phase of CML while few presented in accelerated phase and blast crisis. Bone marrow aspiration and trephine biopsy was done in patients with Non-Hodgkin Lymphomas and Hodgkin Lymphomas to look for bone marrow involvement. Among 82(16.9 %) patients with NHL, 31 patients were showing bone marrow infiltration. Among 35 patients with Hodgkin lymphoma, only 8 patients were having bone marrow involved while no infiltration was seen in the rest.

Acute leukemia was also frequently seen throughout the year. Acute lymphoblastic leukemia was diagnosed in 9.9% (n=48) patients, Acute myeloid Leukemia in 9.3% (n=45) of malignant cases and 7.6% cases (n=36) of acute leukemia were further referred for immunophenotyping by flow cytometry for confirmation. 2 cases of BM infiltration by metastatic tumors and one case of myeloid sarcoma were also diagnosed. Pattern of malignant cases described in table 2.

Table 1: *Diagnostic Outcome of Benign Cases*

Diagnosis	No of cases	Percentage of cases
Aplastic Anemia	48	47.5%
ITP	21	20.8%
Megaloblastic anemia	13	12.8%
Double deficiency Anemia	07	6.9%
Hypersplenism	06	5.9%
Granulomatous disease	03	2.9%
Iron deficiency anemia	01	0.9
Pure red cell aplasia	01	0.9%
Gaucher's Disease	01	0.9%
Total	**101**	**100%**

Table 2: Diagnostic Outcome of Malignant Cases

Dianosis	Subclass	No. of cases	Percentage of cases
CML		148	30.6%
	Chronic phase	122	25.2%
	Accelerated phase	18	3.7%
	Blast crises	07	1.4%
NHL		82	16.9%
	With BM infiltration	31	6.4%
	Without BM infiltration	51	10.5%
ALL		48	9.9%
AML		45	9.3%
	M1	04	0.8%
	M2	20	4.1%
	M3	08	1.7%
	M4	02	0.4%
	M5	01	0.2%
	M6	01	0.2%
	M7	01	0.2%
	Therapy-related	01	0.2%
Acute leukemia		36	7.5%
Hodgkin lymphoma		35	7.2%
	With BM infiltration	08	1.6%
	Without BM infiltration	27	5.6%
Multiple myeloma		22	4.5%
Myelofibrosis		15	3.1%
BM infiltration by atypical infiltrate		14	2.9%
CLL		13	2.7%
MDS		12	2.4%
MPN(unclassified)		04	0.8%
Polycythemia vera		02	0.4%
Essential thrombocythemia		02	0.4%
Metastatic infiltratrion		02	0.4%
CMML		02	0.4%
Myeloid sarcoma		01	0.2%
Total		**483**	**100%**

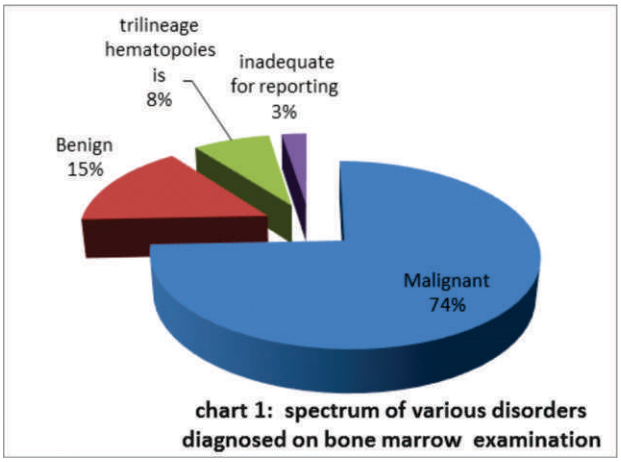


chart 1: spectrum of various disorders diagnosed on bone marrow examination

DISCUSSION

In this study, we evaluated pattern of different benign and malignant disorders diagnosed by BM aspiration and trephine biopsy over a period of 1 year. In our study, median age of presentation was 38 years with male to female ratio of 1.6:1 which is comparable to another study by Manzoor et al, which described spectrum of benign and malignant disorders with a median age of 35 years and M:F ratio of 1.6:1.[1]

Among benign cases, aplastic anemia (47.5%) was found most common in our study. Ahmed et all described in a study at AFIP, Rawalpindi that aplastic anemia is very prevalent in south Asian population.[5] The study stated that genetic factors play a major role in the etiology of aplastic anemia in Asian population because young age, male predilection and higher consanguinity are the major determinants.[5]

In present study, immune thrombocytopenia (ITP) was found second most common benign disorder (20.8%). ITP is an autoimmune disorder caused by the peripheral destruction of platelets. In another study by Tshabalala et al stated that ITP comprise of 4.2% of all cases diagnosed on BM examination.[6] Weycker et al described the Annual incidence of ITP in the US was 6.1/ 100,000, being higher among females as compared to males (6.7 vs. 5.5), and highest among children aged 0–4 years (8.1) and adults aged ≥65 years (13.7). (7) Similar results were also observed in our study, the ITP was seen more frequently in females (n=12) vs males (n=7).

Anemia is a common indication of Bone marrow examination. Megaloblastic anemia was found in 12.8% (n=13), double deficiency in 6.9%

(n=7) and iron deficiency anemia in 0.9%(n=1) of Benign disorders. Manzoor et al in a study in India, showed that double deficiency anemia was most common amongst benign disorders followed by megaloblastic anemia.[1] Nutritional deficiency anemias are very prevalent in our part of the world. In a study at AKUH, Karachi described that vitamin B12 and folate deficiency was found in 52.4% and 50.8% of samples tested respectively from all over Pakistan.[8] Major determinants of nutritional deficiencies are poverty, multiple pregnancies, underweight or overweight and lack of proper diet.[8]

Hypersplenismwas also commonly seen in 5.6 % of patients with benign disorders. Hypersplenism is due to over-activity of spleen leading to removal of RBCs, WBCs and platelets causing cytopenias. In a study by Munir et al stated that hypersplenism was diagnosed n 3.2%of patients.[3] In another study, 29.2% of patients presented with pancytopenia had hypersplenism.[9]

Malignant disorders (74.2%) were far more frequently observed in our study than benign disorders (15.3%). Leukemias are very fatal disorders, timely and definitive diagnosis is essential for early intervention and management. In present study, chronic leukemias (CML=30.6%, CLL= 2.7%) were more prevalent than acute leukemias. In another study conducted in KPK, Pakistan by Ahmed et al, described that acute leukemias (ALL=49.5%, AML= 31.25%) than Chronic Leukemias (CML=10%, CLL = 9.25%).(10) In another study, Ahmed S et al revealed that CML was the most common type of leukemia followed AML, ALL and CLL.[11]

Acute lymphoblastic leukemia (9.9%) was slightly more common than Acute Myeloid Leukemia (9.3%) in present study which is comparable to a study by Nasim et al showed that ALL (49%) is more prevalent than AML (31%).[12] Among AML morphological FAB subtypes, M3 (57%) was more commonly seen followed by M2 (14%), M4 (14%), M1 (7%) and M6 (7%)[12] while in our study, M2 (4.1% of total malignant cases) was most common AML subtype followed by M3 (1.7%), M1 (0.8%). 1 case of therapy related AML was also observed.

In our study among leukemias, chronic myeloid leukemia (CML) was most prevalent comprising of 30.6% (n=148) cases. Most patients with CML presented in chronic phase (CP) 25.2% followed by accelerated phase (AP) 3.7% and blast crisis (BC) 1.4%. These results are comparable to a study conducted in Bangladesh, 86% CML patients presented in CP, 11% in AP and 3% in BC phases.[13] It also stated that patients presented in chronic phase of CML are at younger age with male predominance.[13] Same results were observed by Riaz et al with chro-nic phase of CML observed in 68.9%, AP (15.5%) and BC (6.7%) with a median age of 37.9 years and increased male to female ratio.[14] Usmani et al also describedthat the median age of presentation with CML is quite younger in our part of the world as compared to western literature.[15]

Bone marrow examination was performed in 16.9% (N=82) of patients with Non-hodgkin lymphoma (NHL), out of which 31 patients were having bone marrow infiltration. Comparable to this, Sultan et al described that 31.5% of NHL patients show infiltration of BM.[16] Pattern of infiltration was diffuse (14.6%) predominently, followed by interstitial (6.5%) and paratrabecular (5.4%).[16]

In our study, 7.2% (n=35) patients with Hodgkin lymphoma (HL) were found. Among them, only 8 patients were having bone marrow infiltration. In a study by LONE et al, revealed that 19 out of 50 patients with HL were having BM infiltration.[17] 17 of them were of mixed cellularity type and 2 were of nodular sclerosis type.[16] The pattern of infiltration was interstitial in majority of cases followed by diffuse pattern.[16] Comparable to this, in another study conducted in Turkey, 12.3% of patients with HL show bone marrow infiltration.[18] BM biopsy should be the method of choice for staging because bone marrow examination mostly negative.[18] Bone marrow involvement is common in our area due to late presentation of patients.

Plasma cell dyscrasias are second most common hematological malignancies that range from Mono-

clonal Gammopathy of Unknown Signficance (MGUS) to Plasma cell Leukemia.[19] The disease burden of multiple myeloma in the developing world is not much known. In our study, 4.5% of patient were diagnosed with Multiple myeloma. Plasmacytosis was second most common malignant disorder after leukemias by Manzoor et al.[1] There are many advancements in the diagnosis, monitoring and treatment of MM i.e. autologous stem cell transplant, immunomodulatory agents and proteasome inhibitors have improved the survival.[19]

Myelodysplastic syndrome (MDS) is a clonal disorder characterized by ineffective haemopoesis, peripheral cytopenias and progression to acute myeloid leukemia. MDS was diagnosed in 2.4% (n=20) of patients in our study. MDS is rare in younger population and risk increases with age.[20]

In a study conducted at NIBD Karachi, 52 patients were diagnosed withMDS, with a median age of 60 years and male preponderance (75%).[21] Sultan et al showed similar results with median age 57.6 years and M:F ratio 1.7:1. Among 42 patients, 53.3% had refractory anemia with multi-lineage dysplasia, 22.2% refractory cytopenias with unilineage dysplasia, 4.4% had refractory anemia with excess blasts and 15.5% with MDS unclassified.[1]

Among Myeloproliferative Neoplasm Myelofibrosis was seen in 3.1% (n=15), followed by Polycythemia (0.4%) and Essential thrombocythemia ET (0.4%). Metastatic infiltration was also seen in 2 patients. In adults, metastasis by lung carcinomas are found more frequently followed by breast.[1] Most common presentation with metastatic infil-tration was anemia followed by pancytopenia.[1] Myeloid sarcoma was also found in 1 patient.

CONCLUSION

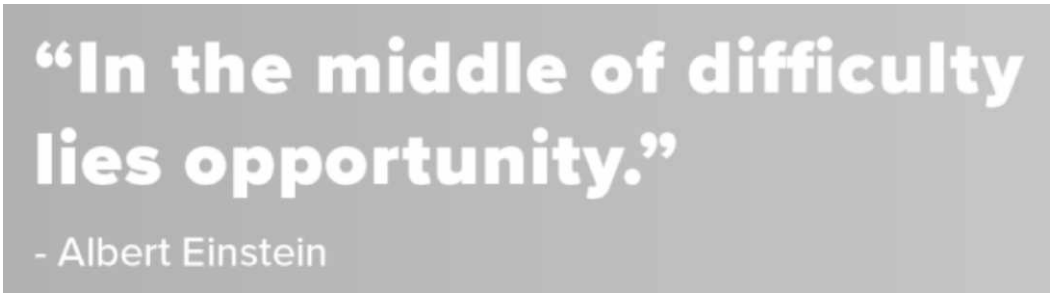
Bone marrow examination is an important tool to diagnose various benign and malignant disorders involving bone marrow. Malignant disorders including leukemias, lymphomas and plasma cell dyscrasias were found more frequently in our study. Techniques like flow-cytometry, immunohistochemistry and cytogenetics should be used for confirmation and further classification.

REFERENCES

1. Manzoor, F., Bhat, S., Bashir, Y. and Geelani, S., 2018. Diagnostic Outcome of Bone Marrow Aspiration– An Experience from Tertiary Care Hospital. Journal of Medical Science And clinical Research, 6(8).
2. Gilotra, M., Gupta, M., Singh, S. and Sen, R., 2017. Comparison of bone marrow aspiration cytology with bone marrow trephine biopsy histopathology: An observational study. Journal of Laboratory Physicians, 9(03), pp.182-189.
3. Munir AH, Qayyum S, Gul A, Ashraf Z. Bone marrow aspiration findings in a tertiary care hospital of Peshawar . J Postgrad Med Inst 2015; 29(4): 297-300
4. Majumdar A, Wasim NA, Jana A, Biswas S, Bhattacharyya, Diagnostic outcome of bone aspiration in a paediatriccentre in Kolkata, India. Indian J Health Sci Biomed Res 2015;8;125-9
5. Ahmed P, Chaudhry Q, Satti T, Mahmood S, Ghafoor T, Shahbaz N et al. Epidemiology of aplastic anemia: a study of 1324 cases. Hematology. 2020;25(1):48-54.
6. Tshabalala WS, Pillay S, Wilson DPK. Diagnostic outcomes of bone marrow aspirate and trephine biopsies performed at a hospital in KwaZulu-Natal, South Africa. Afr J Lab Med. 2020;9(1), a1028. https://doi.org/10.4102/ajlm.v9i1.1028
7. Weycker D, Hanau A, Hatfield M, Wu H, Sharma A, Bensink M et al. Primary immune thrombocytopenia in US clinical practice: incidence and healthcare burden in first 12 months following diagnosis. Journal of Medical Economics. 2019;23(2):184-192.
8. Soofi S, Khan G, Sadiq K, Ariff S, Habib A, Kureishy S et al. Prevalence and possible factors associated with anaemia, and vitamin B12 and folate deficiencies in women of reproductive age in Pakistan: analysis of national-level secondary survey data. BMJ Open. 2017;7(12):e018007.
9. Jain A, Naniwadekar M. An etiological reappraisal of pancytopenia - largest series reported to date from a single tertiary care teaching hospital. BMC Blood Disorders. 2013;13(1).
10. Ahmad S, Kifayatullah, Shah K, Hussain H, Haq A, Ullah A et al. Prevalence of Acute and Chronic Forms of Leukemia in Various Regions of Khyber Pakhtunkhwa, Pakistan: Needs Much More to be

done!. Bangladesh Journal of Medical Science. 2019;18(2):222-227.

11. Ahmad S, Tandon N, Tiwari N, Mehdi S, Zaidi N, Zaidi Z. Frequency of Different Types of Leukemia in Bone Marrow- Study at a Tertiary Care Center, Lucknow. British Journal of Medicine and Medical Research. 2016;17(10):1-7.
12. Nasim N, Malik K, Malik N, Mobeen S, Awan S, Mazhar N. Investigation on the prevalence of leukaemia at a tertiary care hospital, lahore. Biomedica. 2013;29(January- March 2013).
13. Mottalib, M.A., Sultana, T.A., Khalil, M.I. et al. Phase distribution of chronic myeloid leukemia in Bangladesh. BMC Res Notes 7, 142 (2014). https://doi.org/10.1186/1756-0500-7-142
14. Ahmed R, Naqi N, Hussain I, Khattak BK, Nadeem M, Iqbal J. Presentating phases of chronic myeloid leukaemia. J Coll Physicians Surg Pak. 2009 Aug; 19(8): 469-72. PMID: 19651006.
15. Usmani S, Yunus s, Jamal Y. Overview of Chronic Myeloid Leukemia Patients in Pakistan in the Pre-Imatanib Era, Asian Pacific Journal of Cancer Prevention,. 2009;10.
16. Sultan S, Baloch N, Ahmed ZA, Irfan SM, Parveen S. Pattern of bone marrow involvement in non Hodgkin's lymphoma classified according to WHO classification: Report of a developing country Pakistan. J Lab Physicians. 2018 Jan-Mar;10(1):17-20. doi:10.4103/JLP.JLP_9_17. PMID:29403198; PMCID: PMC5784286
17. Lone A, Naeem S. Frequency and pattern of bone marrow infiltration in hodgkin's lymphoma. Biomedica. 2011;27(Jul-Dec):132-135.
18. Sudalaimuthu M, Basu D. Clinicopathological features of bone marrow infiltration in hodgkin lymphoma. should bone marrow staging be done only in high risk patients?. Turkish Journal of Pathology. 2017;.
19. Kazandjian D. Multiple myeloma epidemiology and survival: A unique malignancy. SeminOncol. 2016 Dec;43(6):676-681. doi:10.1053/j.seminoncol. 2016. 11.004. Epub 2016 Nov 10. PMID: 28061985; PMCID: PMC5283695.
20. Mohammad AA. Myelodysplastic syndrome from theoretical review to clinical application view. Oncol Rev. 2018 Dec 7;12(2):397. doi: 10.4081/ oncol. 2018.397. PMID: 30607219; PMCID: PMC 6291758
21. Taj M, Maqsood S, Shamsi T. Myelodysplastic Syndromes in Pakistani Population-Analysis of 52 Cases and their Outcome on Best Available Treatment Options. Hematology & Transfusion International Journal. 2015;1(4).
22. Sultan S, Irfan S, Jawed S. Spectrum of the WHO Classification De Novo Myelodysplastic Syndrome: Experience from Southern Pakistan. Asian Pacific Journal of Cancer Prevention. 2016; 17(3): 1049-1052.



MYOINOSITOL AS AN EFFECTIVE AGENT FOR SUBFERTILE FEMALES WITH POLYCYSTIC OVARIAN SYNDROME

Mahpara Shaukat,[1] Safia Parveen,[2] Hina Ilyas,[3] Zareen Amjad[4] Mudassar Aslam,[5] H.M. Amjad[6]

How to cite: Shaukat M, Parveen S, Ilyas H, Amjad Z, Aslam M, Amjad HM. Myoinositol as an effective agent for subfertile females with polycystoc ovarian syndrome. JAIMC. 2021; 19(1): 173-177.

Abstract

Background: Sub fertility is one of the common problems across the world and Poly-cystic ovarian syndrome is the most common contributory factor to this sub fertility.

Objective: To observe the effectiveness of myoinositol in subfertile female with polycystic ovarian syndrome.

Methodology: It was an experimental study conducted at Obstetrics& Gynaecology Department of DHQ Teaching Hospital, Sahiwal from June 2016 to March 2019. Seventy subfertile patients who fulfilled Rotterdam criteria of polycystic ovarian syndrome were recruited.

Results: The mean age of the women achieving pregnancy or not was not statistically different. 11 of the subjects were non-compliant while 8 subjects lost to follow up. Over all clinical pregnancy rate was 74.50%. All patients having primary subfertility conceived after treatment while only 43.48% of the secondary subfertility could conceive. Subjects with secondary subfertility were older in age and had longer mean duration of subfertility. 40% of the secondary subfertile females and 14.23% of the primary subfertile females could not successfully complete the pregnancy.

Conclusion: Current study shows significant improvement in clinical pregnancy rate in subfertile women with polycystic ovarian syndrome after treatment with myoinositol. So it is highly effective for the treatment of subfertility.

Key Words: Primary subfertility, Secondary subfertility, Clinical Pregnancy, Rotterdam criteria

Subfertility is one of the common problems across the globe having significant social and psychological impact on patient's life.[1] World Health Organization (WHO) has defined infertility as failure to conceive after 12 months or more of regular un-protected sexual intercourse in married couples.[2] Weight, dietary habits, psychological stress, use of alcohol, caffeine and over-the-counter drugs, environmental exposures and cigarette smoking are some modifiable factors having significant impact on subfertility.[3] Primary subfertility is when a couple is unable to conceive even a single time whereas in secondary subfertility, couples have conceived at least once before.[4] Primary infertility is associated with increasing maternal age[5] while common causes of secondary subfertility include maternal age, marriage duration and socio-economic status of the family.[6]

Prevalence rate and type of subfertility is reported to be variable across various regions.[7] Prevalence of primary and secondary subfertility from a population based in China is reported to be 9.5% and 6% respectively. The figures are a little high (primary 25% & secondary 9.7%) for those women who were actively trying to become pregnant.[8] Contrary to this, prevalence of secondary subfertility is reported to be more than ten-fold higher than primary

1. Mahpara Shaukat
2. Safia Parveen
3. Hina Ilyas
4. Zareen Amjad
5. Mudassar Aslam
6. H.M.Amjad

1-4,6. Sahiwal Medical College and Hospital Sahiwal
5. PGMI / AMC / LGH,Lahore

Correspondence:
Dr. Mahpara Shaukat, *Assistant Professor Obstetrics & Gynecology,*
E- mail: doctor.doctor01@yahoo.com

Submission Date: 03-10-2020
1st Revision Date: 9-11-2020
Acceptance Date: 18-11-2020

subfertility from Suizhong county China.[9] The prevalence of infertility in Pakistan ranges from 7% to 12% in married couples. Male subfertility is more common than female subfertility.[10,11]

Polycystic ovarian syndrome (PCOS) is a prevalent reproductive disorder in women of child bearing age. 70 to 80% of the women with PCOS may have one or other type of infertility.[12] Community based studies have reported higher number of couples seeking fertility treatment with female partner having PCOS.[13] Prevalence of PCOS ranges from as low as 5.6% in Chinese population to as high as 16% in Middle East countries.[14] Prevalence of subfertility in PCOS women is reported to be 15 fold higher than non-PCOS subjects. Similarly, use of hormonal treatment is significantly higher in PCOS patients.[15]

Myoinositol (MI) is a natural compound found in many fruits, beans and nuts and regulates secretion of ovary and other exocrine glands. It is considered as a safe supplement for IVF treatment in PCOS women due to less side effects and significant improvement of metabolic parameters of the patients.[16] MI is considered as one of the safest treatment for subfertility but is always not effective in treating PCOS and other related conditions. Combination of other ovulation induction agents like metformin and clomiphene citrate has added effect and significantly improves fertility rate in patients.[17,18] Varying response to Myo-inositol therapy in individuals has been reported.[17] A good number of couples seek sbfertility treatment in Pakistan due to social constraints. Little is known about the utility of myoinositol for the treatment of infertility in our population. The current study was planned to observe the effectiveness of myoinositol for the treatment of sub-fertile PCOS females in our population.

METHODOLOGY

This was an experimental study conducted at department of Obstetrics and Gynecology, Sahiwal Medical College teaching hospital Sahiwal from June 2016 to March 2019. During the study period, 70 subfertile women having poly-cystic ovarian syndrome as defined by Rotterdam classification were treated with 1000mg of myo-inositol twice daily. Women having any known reproductive or endocrine disorder other than PCOS were excluded from the study. Couples with subfertility in both partners and women with subfertility of unexplained origin were also excluded from the study. The end points of the study were either completion of 6 months of treatment with myo-inositol or conception of the women whichever was earlier. The primary outcome of the study was to estimate the clinical pregnancy rate in females undergoing MI treatment. The secondary outcome measure was to check outcome of the pregnancies in these patients. Patients who were non-compliant to the treatment or lost to follow-up were excluded from the study. All the subjects included in the study were given metformin and clomiphene citrate as combination therapy.

RESULTS

A total of 70 females fulfilling the inclusion criteria were included in the study. 11 of the subjects were non-compliant while 8 subjects lost to follow up. 51 women meeting primary end-point were evaluated out of which 38 (74.50 %) subjects conceived. The mean age of the women achieving clinical pregnancy or not was not statistically different. Duration of infertility was significantly high in women not conceiving with myoinositol treatment.

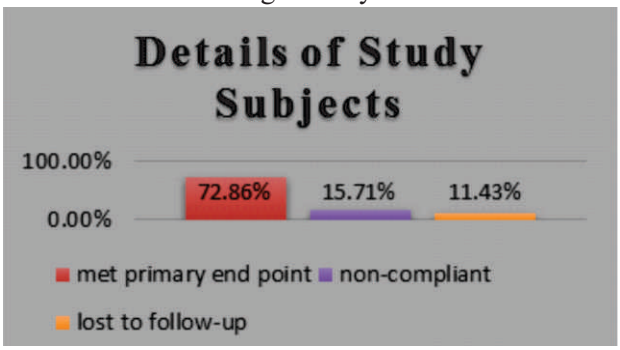


Fig1: *Comparison between Subjects on the Basis of Status*

Subjects with secondary infertility were older in age and have longer mean duration of fertility

Table 1: Comparison between Subjects on the Basis of Status of Clinical Pregnancy

Clinical pregnancy	
	No (n = 13)
29.68 + 4.31	29.85 + 5.73
2.43 + 0.95	3.6 + 1.98
3.53 + 1.18	6.00 + 0.00

(Table 2).

All the patient having primary infertility and treated with MI had clinical pregnancy while only 10

Table 2: Comparison between Subjects on the Basis of Types of Infertility

	Type of infertility	
	Primary (n = 28)	Secondary (n = 23)
Age of the Patient	27.75 + 4.30	32.13 + 3.94
Duration of infertility (years)	2.55 + 1.39	2.95 + 1.33
Treatment duration with myo-inositol (months)	4.21 + 1.57	4.09 + 1.41

(43.48%) of the secondary subfertility could conceive. 40% of the secondary subfertile females and 14.23% of the primary subfertile females could not successfully complete the pregnancy (Fig. 2).

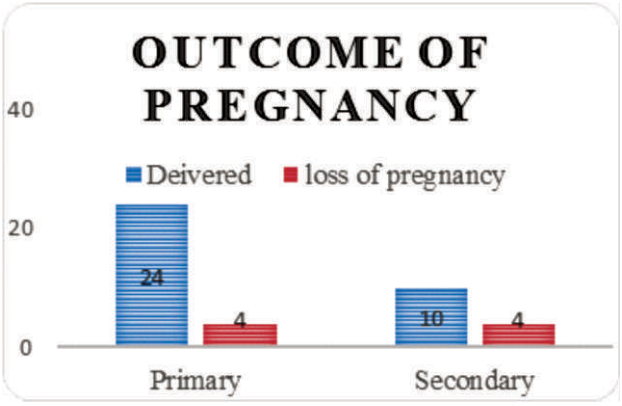


Fig 2: *Outcome of Pregnancy*

DISCUSSION

Polycystic ovarian syndrome is an endocrine disorder and leads to subfertility in patients. Subfertility is a prevalent disease across the globe and have significant social repercussions, societal corollaries and personal suffering. It can adversely affect the psychological health and marital relationship of the couples. Couples with primary subfertility seek medical treatment earlier than secondary subfertile couples due to sheer peer pressure. Myo-inositol, metformin, clomiphene citrate and gonadotrophins are routinely used for the treatment of subfertility. Mean age of the females seeking subfertility treatment in the study was 29.73+4.65 years. Mean duration of subfertility was 2.73+1.37 years while average treatment duration was 4.16 + 1.19 years. 74.51% of the subjects became pregnant with mean treatment duration of 3.29 + 1.41years.

More than half of the patients (54.90%) were having primary subfertility while 45.10% reported secondary subfertility. A decline in female fertility has been observed with advanced age. Review of the literature suggests that primary aim of the subfertility treatment in women is to improve number and quality of the oocytes and embryos. A number of probable mechanisms have been suggested by the researchers including increasing insulin sensitivity, improving glucose uptake and restoring hormonal profile and ovulatory status of the PCOS females.[19] Administration of myoinositol decreases serum insulin levels in obese PCOS patients but effect is statistically significant only in patients high insulin levels.[20] MI has been shown to significantly improve embryo quality and fertilization rate in women with PCOS undergoing ART cycles.[21] Studies have also reported positive metabolic and hormonal changes with MI supplementation. Statistical significant changes in lipid levels, insulin, DHEAS, testosterone level and systolic and diastolic blood pressure have been observed.[22]

Variable results are observed in studies with myoinositol supplementation. A retrospective study from Germany reported clinical pregnancy in 15.1% of the patients treated with daily supplementation of myoinositol and folic acid.[23] Another study reported ovulation induction in 61.7% of the study subjects following treatment with MI. Combination of clomiphene citrate and myoinositol has better results in ovulation induction and pregnancy rate than MI alone.[17] Recently, results of randomized controlled trial showed a high pregnancy and live birth rate with

use of combination of Myo and D-chiro-inositol in women with PCOS undergoing ICSI for subfertility treatment.[24] Another study comparing efficacy of metformin and myoinositol in sub fertile PCOS females reported higher number of pregnancy in Myo-inositol group.[25]

Metformin has also been used successfully for the treatment of anovulation and subfertility in PCOS patients. Ovulation induction in approximately 50% of the patients is observed. Considerably, higher rates are achieved when clomiphene citrate is combined with metformin.[26] Results of our study are highly promising for use of myoinositol, metfor-min and clomiphene citrate in primary and secon-dary subfertile patients with PCOS. Previously, researcher have reported higher pregnancy rate in patients treated with combination of MI and clomiphene citrate. Rolland et al. reported cumulative pregnancy rate of 53.8% with combination therapy compared to 42.2% with clomiphene citrate only.[18] Another study reported cumulative ovulation rate of 89% and 36% of the ovulatory women became pregnant.[17]

Much lower ovulatory and pregnancy rate in other studies may be due to a number of factors. Some of these include characteristics of the cohort, interventions used, frequency of primary and secondary sub fertility among subjects and causes of subfertility. Moreover, previously studies have used MI either in combination with clomiphene citrate or metformin. Probably myoinositol, clomiphene citrate and metformin have synergistic effects with each potentiating beneficial effects of other drugs in PCOS patients. The variability in literature and highly promising results of the current study provides new opportunities to find the effects of these in PCOS patients. Further large scale clinical studies should be planned to validate the results of the current study and implementation of treatment strategy in PCOS patients.

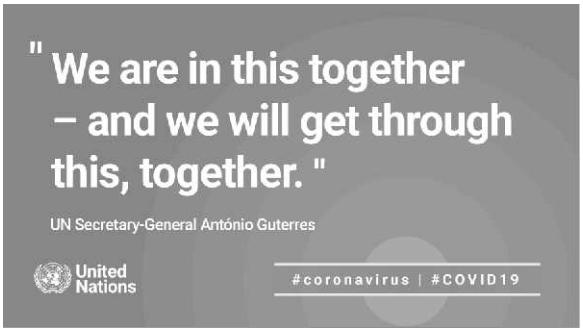
CONCLUSION

Current study shows significant improvement in clinical pregnancy rate in sub fertile women with polycystic ovarian syndrome after treatment with myoinositol. So it is highly effective for the treatment of sub fertility.

REFERENCES

1. Sarac M, Koc I. Prevalence and risk factors of infertility in TURKEY: Evidence from demographic and health surveys, 1993–2013. J Biosoc Sci. 2017; 50(4):472-90.
2. World Health Organization. Sexual and reproductive health: Multiple definitions of infertility 2016 [cited 2019 16 Jun]. Available from: https://www.who.int/reproductivehealth/topics/infertility/multiple-definitions/en/.
3. Sharma R, Biedenharn KR, Fedor JM, Agarwal A. Lifestyle factors and reproductive health: taking control of your fertility. Reprod Biol Endocrinol. 2013;11:66.
4. Tabong PT, Adongo PB. Infertility and childlessness: a qualitative study of the experiences of infertile couples in Northern Ghana. BMC Pregnancy Childbirth. 2013;13:72.
5. Kazemijaliseh H, Ramezani Tehrani F, Behboudi-Gandevani S, Hosseinpanah F, Khalili D, Azizi F. The prevalence and causes of primary infertility in Iran: A population-based study. Glob J Health Sci. 2015;7(6):226-32.
6. Benksim A, Elkhoudri N, Addi RA, Baali A, Cherkaoui M. Difference between primary and secondary infertility in Morocco: frequencies and associated factors. Int J Fertil Steril. 2018;12(2):142-6.
7. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Med. 2012; 9(12):e1001356.
8. Zhou Z, Zheng D, Wu H, Li R, Xu S, Kang Y, et al. Prevalence of infertility in China: a population based study. Fertility and Sterility. 2017; 108(3): e114.
9. Cong J, Li P, Zheng L, Tan J. Prevalence and risk factors of infertility at a rural site of Northern China. PLOS ONE. 2016;11(5):e0155563.
10. Rahim R, Majid SS. Aetiological factors of infertility. JPMI. 2004;18(2):166-71.
11. Shaheen R, Subhan F, Sultan S, Subhan K, Tahir F. Prevalence of infertility in a cross section of Pakistani population. Pakistan J Zool. 2010;42(4):389-93.

12. Melo AS, Ferriani RA, Navarro PA. Treatment of infertility in women with polycystic ovary syndrome: approach to clinical practice. Clinics (Sao Paulo). 2015;70(11):765-9.
13. E. JA, J. TH, Sanjeeva R, Sophia Z, Jacqueline B. Prevalence of infertility and use of fertility treatment in women with polycystic ovary syndrome: Data from a large community-based cohort study. J Womens Health. 2015;24(4):299-307.
14. Ding T, Hardiman PJ, Petersen I, Wang F-F, Qu F, Baio G. The prevalence of polycystic ovary syndrome in reproductive-aged women of different ethnicity: a systematic review and meta-analysis. Oncotarget. 2017;8(56):96351-8.
15. Joham AE, Teede HJ, Ranasinha S, Zoungas S, Boyle J. Prevalence of infertility and use of fertility treatment in women with polycystic ovary syndrome: Data from a large community-based cohort study. J Womens Health. 2015;24(4):299-307.
16. Regidor P-A, Schindler AE. Myoinositol as a safe and alternative approach in the treatment of infertile PCOS women: A German observational study. Int J Endocrinol. 2016;2016:5.
17. Kamenov Z, Kolarov G, Gateva A, Carlomagno G, Genazzani AD. Ovulation induction with myo-inositol alone and in combination with clomiphene citrate in polycystic ovarian syndrome patients with insulin resistance.Gynecol Endocrinol. 2015; 31(2): 131-5.
18. Rolland AL, Peigne M, Plouvier P, Dumont A, Catteau-Jonard S, Dewailly D. Could myo-inositol soft gel capsules outperform clomiphene in inducing ovulation? Results of a pilot study. Eur Rev Med Pharmacol Sci. 2017;21(2 Suppl):10-4.
19. Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, et al. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. Human Reproduction Update. 2016;22(6):687-708.
20. Genazzani AD, Prati A, Santagni S, Ricchieri F, Chierchia E, Rattighieri E, et al. Differential insulin response to myo-inositol administration in obese polycystic ovary syndrome patients. Gynecol Endocrinol. 2012;28(12):969-73.
21. Akbari Sene A, Tabatabaie A, Nikniaz H, Alizadeh A, Sheibani K, Mortezapour Alisaraie M, et al. The myo-inositol effect on the oocyte quality and fertilization rate among women with polycystic ovary syndrome undergoing assisted reproductive technology cycles: a randomized clinical trial. Archives of Gynecology and Obstetrics. 2019;299(6):1701-7.
22. Costantino D, Minozzi G, Minozzi E, Guaraldi C. Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. Eur Rev Med Pharmacol Sci. 2009; 13(2): 105-10.
23. Regidor P-A, Schindler AE. Myoinositol as a Safe and Alternative Approach in the Treatment of Infertile PCOS Women: A German Observational Study. International Journal of Endocrinology. 2016; 2016: 5.
24. Mendoza N, Diaz-Ropero MP, Aragon M, Maldonado V, Llaneza P, Lorente J, et al. Comparison of the effect of two combinations of myo-inositol and D-chiro-inositol in women with polycystic ovary syndrome undergoing ICSI: a randomized controlled trial. Gynecological Endocrinology. 2019:1-6.
25. Raffone E, Rizzo P, Benedetto V. Insulin sensitiser agents alone and in co-treatment with r-FSH for ovulation induction in PCOS women. Gynecological Endocrinology. 2010;26(4):275-80.
26. Tang T, Norman RJ, Balen AH, Lord JM. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Cochrane Database of Systematic Reviews. 2003(2).



THE IMPACT OF SIX WEEKS OF ADMINISTRATION OF AJWA SEED AND FRUIT ON RENAL BIOCHEMICAL INDICATORS IN RAT MODEL OF ALLOXAN-INDUCED DIABETIC NEPHROPATHY

Iram Imran,[1] Imran Maqsood Butt,[2] Ajmal Afzal,[3] Sadia Chiragh[4]

How to cite: Imran I, Butt IM, Afzal A, Chiragh S. The impact of six week of administration of ajwa seed and fruit on renal biochemical indicators in rat model of alloxan-induced diabetic nephropathy. JAIMC. 2021; 19 (1): 178-184.

Abstract

Background: Natural products are being used as an important source for exploring new drugs. Phoenix dactylifera has been used traditionally for the treatment of diseases caused by oxidative stress.

Objective: To investigate the nephroprotective activity of seed and fruit of P. Dactylefera (Ajwa variety) in the rat model of alloxan-induced diabetes mellitus. It was an experimental study, conducted in Post Graduate Medical Institute in a period of six months.

Methodology: Random allotment of 32 male rats was done in 4 groups having 8 rats in each group. Group 1 was treated as normal control. Group 2, 3 & 4 were challenged intraperitoneally with alloxan monohydrate to induce diabetes mellitus. After the establishment of diabetes, Group II was treated as diabetic control and Group 3 and 4 were treated with Ajwa seed and flesh diet for 6 consecutive weeks. Body weight, fasting blood glucose (FBG), serum urea & creatinine, microalbuminuria, urine creatinine and creatinine clearance were estimated at 0 and 6 weeks.

Results: The data showed that Ajwa date seed significantly ameliorated hyperglycemia but did not normalize the fasting blood glucose. We found exceedingly significant improvement in body weight, renal serum and urine parameters with Ajwa seed suggesting lessening in diabetic nephropathy. The effect with fruit diet was much lesser than seed.

Conclusion: Our study results showed that Phoenix dactylefera possesses a significant nephroprotective effect in diabetes mellitus.

Key Words: Diabetic nephropathy, Ajwa date seed, Diabetes mellitus, Hyperglycemia;

Hyperglycemia is believed as one of the most promising causes of chronic kidney disease. International diabetes federation states that there are 451 million diabetics worldwide and this figure will augment up to 693 million in the next 25 years. Eighty percent of such problems come from developing countries especially from the younger population.[1]

In the South Asia region, diabetes has quickly developed into the most important health problems. Key determinants are urbanization, life-style changes, industrialization and globalization. Pakistan is the main contributor to this load.[2]

It has been concluded from several published studies that the primary reason for complications from diabetes is oxidative stress. Oxidative stress during diabetes directs the appearance of free radicals in the body along with less synthesis of defensive enzymes which ultimately results in malfunctioning of the human tissues and organs if not treated well.[3]

Alloxan monohydrate is one of the most adopted methods for inducing diabetes and its related complications. Oxidative stress produced by alloxan

1. Iram Imran
2. Imran Maqsood Butt
3. Ajmal Afzal
4. Sadia Chiragh

1. Central Park Medical College, Lahore
2. Rashid Latif Medical College, Lahore
3. Gujranwala Medical College, Gujranwala
4. Al Aleem Medical College, Gulab Devi Hospital, Lahore

Correspondence:
Dr. Iram Imran, *Assistant Professor Pharmacology& Therapeutics, Central Park Medical College Lahore, Pakistan*
E-mail: iramimran49@gmail.com

Submission Date: 27-09-2020
1st Revision Date: 12-10-2020
2nd Revision Date: 18-10-2020
Acceptance Date: 22-10-2020

results in severe hyperglycemia leading to renal complications of the disease in animals.[4]

Versatile antioxidants have played an important role in increasing the defense enzymes of the body against oxidative stress and in this way protecting kidneys from the nephropathic condition. Hence the herbs, plants and fruits with multi-use antioxidant properties are receiving more interest.[5]

Protection against multiple diseases by Phoenix Dactylifera (palm date) especially its seeds and fruits has confirmed its antioxidant properties.[6] Fruits of Ajwa are loaded with carotenoids, phenolics, flavonoids and dietary fibers. The highest amount of crude protein (2.94%) is found in Ajwa flesh while pits contain the highest insoluble dietary fiber (34.6%). Ajwa seeds are the greatest source of zinc (1.91mg/g) and fruit supplies the highest concentration of magnesium(1.5mg/g) and potassium (6.45mg/g).[7]

The phenolic content of Ajwa fruit ranges between 245mg and 455 mg/100g. Major phenols include derivatives of gallic, caffeic, coumaric and ferulic acid. The flavonoids content of Ajwa date fruit is 2.7mg/100g and major flavonoids are rutin (6.50mg/kg), catechin (7.30mg/kg) and luteolin.[8] Phenols in date seeds are absorbed very easily, and are in large quantity than in fruit. Quercetin (1.3mg/100g) and iso-quercitin are the major flavonoids present in seeds.[9] The polyphenolics & flavonoids present in fruit and pits have immense antioxidant and free radical scavenging properties.[10]

The anti-hyperglycemic effect of aqueous extract of Phoenix Dactylifera seed and its possible mechanism through increased production of insulin has been demonstrated in a few studies.[11]

In a very recent study researchers reported a decrease in fasting blood sugar level, serum urea and creatinine along with amelioration of histological changes in kidneys of diabetic rats after oral administration of Hayani date seed extract.[12]

The flesh of Ajwa date has also been tested for its ameliorative effects on renal function and tubular damage by Ocratoxin.[13] In our own previous studies, we have confirmed the antihyperglycemic[14] as well as antinephropathic potential of ajwa seed in 4 weeks.[15] The effect of flesh was far less than seed, so keeping in view the highest levels of antioxidants in Ajwa date, we decided to design a study with six weeks duration in which we administer Ajwa seed and flesh for 6 weeks in alloxan induced diabetic nephropathic rats to see their further potential .

METHODOLOGY

Two kg whole Ajwa date was purchased from Aseel market Madina Munawara (Saudi Arabia). The date was identified by the Botany Department, Government College University Lahore. A voucher specimen number GC.Herb.Bot.2954 was allotted. The seeds were separated from the fruit and washed. Air-dried seeds were ground and stored in air tight containers with label on it. The fruit was squashed finely. Ground seeds (1.5 g) or fruits (7grams) were mixed with 100gram rat feed separately and pellets were made for animals of groups 3 & 4 respectively. The feed was prepared fresh at one week intervals and stocked at a dry place. This each day rat feed requirement was planned on the basis of 7 dates daily recommendation for an adult human as referred in Ahadith16 and supplied ad libitum.

Thirty-two healthy male rats, weighing 120-150g were bought from the University of Veterinary and Animal Sciences Lahore. It was a randomized/control study so the animals were randomly placed into four groups using lottery technique having 8 rats in each group. All animals were kept in the animal house, Post Graduate Medical Institute, Lahore. The controlled environment temperature was maintained at 23°C with an alternating 12 h light and day cycle. They were given regular pellet diet and water ad libitum. The study was approved by the Ethical Committee of Post Graduate Medical Institute, Lahore.

Alloxan (Sigma USA) was freshly dissolved in normal saline just before use and given as a single intraperitoneal injection (150mg/kg) to fasting rats

of all groups except normal control. After about 72 hours, animals showing blood glucose fasting level >250 and < 500 were chosen as diabetics and divided into four groups for study.

Group 1 (normal control) rats were given normal saline by single intraperitoneal injection. Diabetes was induced in Group 2, 3 and 4 as mentioned above Group 2 was reserved as a diabetic control group. Animals of group 3 and 4 were given Ajwa seed and flesh diet respectively for six weeks after affirmation of diabetes.

Blood samples of animals were collected after overnight fasting by performing cardiac puncture and 24-hour urine sample was also collected at 0 and 6 weeks. Fasting blood glucose, serum urea, creatinine and urine creatinine was assessed using the enzymatic method by commercial kits (Crescent diagnostic). Microalbuminuria was evaluated by the log logit method (Randox diagnostics). Creatinine clearance was calculated using formula.

Data was analyzed by SPSS16 and expressed as mean±SD. One way analysis of variance (ANOVA) and Tukey's test was applied to see the difference between the groups and multiple comparisons respectively. $p<0.05$ was considered statistically significant. Values at week 6 were used for statistical comparison.

RESULTS

Treatment with Ajwa seed nearly normalized weight of diabetic rats.

Body weight was found significantly decreased (p 0.001) in the diabetic group in comparison to the control group. We found that treatment with Ajwa seeds significantly (p 0.01) improved body weight as compared with the diabetic group. Treatment with Ajwa fruit least restored body weight and remained significantly different from seed group (Table 1).

Table 1: Treatment with Ajwa seed nearly normalized body weight and fasting blood glucose. Data is presented as Mean±SD where n=8. *, ** and ***statistical difference as compared to control at $p<0.05$, $p<0.01$ and $p<0.001$ respectively. #, ## and ### statistical difference as compared to diabetic control group at $p<0.05$, $p<0.01$ and $p<0.001$ respectively.

An increase in fasting blood glucose was found significantly (p 0.001) in treatment groups as compared with control groups. We found that the Ajwa seed diet highly significantly attenuated hyperglycemia (p 0.001). Similarly Ajwa fruit also significantly ameliorated fasting blood glucose levels in diabetic rats when compared to the positive control group (Table 1).

We found a significant (p 0.001) increase in urea and creatinine levels in serum while microalbuminuria levels in the urine of diseased groups. Treatment with Ajwa seed showed a highly significant decrease (all p 0.001) in all parameters when compared with the diabetic control group. Similarly the Ajwa flesh treated group also showed a significant decrease (p 0.01) in serum parameters and microalbuminuria (p 0.05) as compared with the diabetic group (Figure 1).

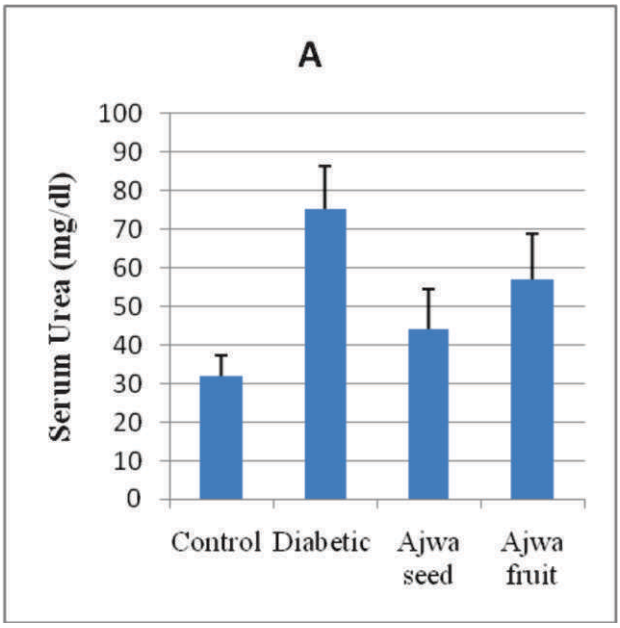
Regarding urinary renal profile, urine creatinine and creatinine clearance levels showed a marked decrease (p-value 0.001) in the diseased group. Treatment with Ajwa seed highly significantly (all p 0.001) improved the renal profile as compared to the diabetic group. Similarly, treatment with Ajwa fruit also showed significant enhancement with p values of 0.01 and 0.05 for urinary creatinine and creatinine clearance respectively (Table 2).

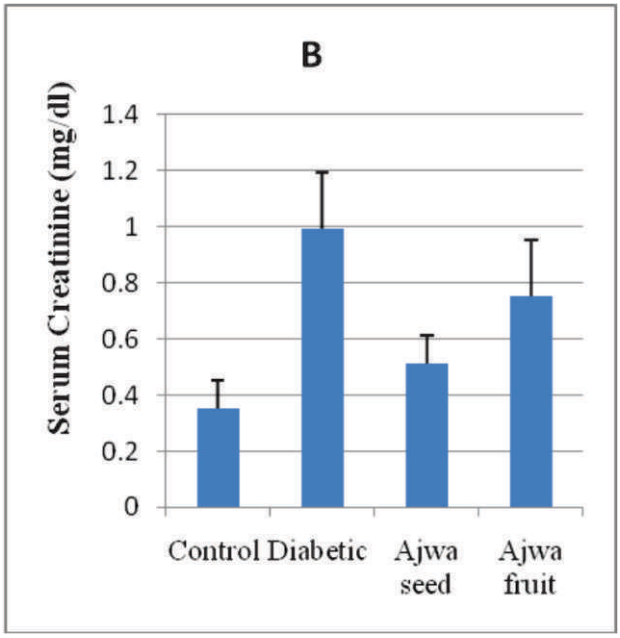
Table 2: Treatment with both Ajwa seed and fruit enhanced urinary creatinine and creatinine

Table 1: *Body Weight and Fasting Blood Glucose (Week 6)*

Parameters	Group 1 (Normal Control)	Group 2 (Diabetic Control)	Group 3 (Ajwa seed)	Group 4 (Ajwa fruit)
Body weight	230.1±9.1	143.9±21.7***	190.6±30.4##	156.4±31.0#
Fasting blood glucose	90.0±5.3	354.0±68.0***	182.4±67.7###	248.4±65.9##

clearance levels. Data is presented as Mean±SD where n=8. ** and ***statistical difference as compared to control at p<0.01 and p<0.001 respectively. ## and ### statistical difference as compared to the diabetic control group at p<0.01 and p<0.001 respectively.





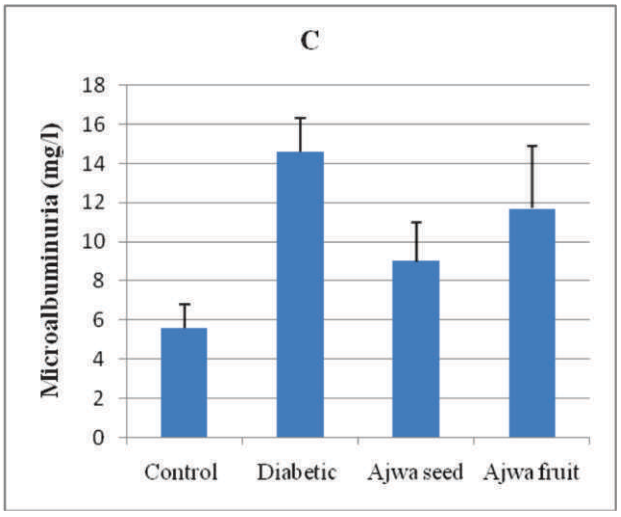


Fig. 1: *Treatment with Ajwa seed and fruit both significantly improved serum urea (A), serum creatinine (B), and microalbuminuria (C). Mean±SD is given to indicate the data where n=8. ***statistical difference as compared to control at p<0.001. #, ## and ### statistical differences as compared to diabetic control group at p<0.05, p<0.01 and p<0.001 respectively.*

DISCUSSION

Conventionally Ajwa dates have been consumed by people for its tremendous benefits but few studies have conducted to explore its antidiabetic potential and its favorable effects on complications of diabetes mellitus.

Abdelaziz , in his latest 4 weeks study confirmed that seed suspension of P dactylefera (Hayani) has antihyperglycemic and nephroprotective potential in rats where diabetes was induced by streptozotocin and further concluded that these effects may be ascribed to improved oxidative stress through versatile antioxidants, effectual phenols and their ability to inhibit antioxidative enzymes.[12]

The current study was conducted to explore the effects of Ajwa date seed and fruit on nephropathy in

Table 2: *Urinary Creatinine & Creatinine Clearance (Week 6)*

Urinary Parameters	Group 1 (Control)	Group 2 (Diabetic Control)	Group 3 (Ajwa seed)	Group 4 (Ajwa fruit)
Urinary creatinine (mg/dl)	19.0±1.3	7.0±1.6***	11.7±1.7###	9.4±1.1##
Creatinine clearance (ml/min)	0.234±0.04	0.055±0.01***	0.178±0.03###	0.092±0.01#

rats induced through intraperitoneal administration of alloxan monohydrate.

In the present study, we found that the growth of animals declined in diabetic control groups after 6 weeks in contrast to normal control rats. These results are in concurrence with earlier studies which demonstrated that hyperglycemia results in decreased growth and rigorous muscle wasting due to accelerated degradation of tissue proteins.[17]

Oral administration of the Ajwa seed diet significantly improved growth and body weight gain in contrast to diabetic control rats.

Our results revealed that this enhancement in weight may possibly be justified by remarkable glycemic control attained by the Ajwa seed diet. Our study results are in accordance with previously published research by Abdelaziz who verified that date seed suspension increases the oxidative enzymes of the body and significantly reduces blood glucose levels (approx 50%) and enhances the weight of diabetic nephropathic rats.[12] Shadab Ahmad et al[18] also advocated that orally given date fruit suspension (Aseel variety) reduced intense hyperglycemia in alloxanized diabetic rats. The dietary fiber and fructose in date with a low glycemic index reduces the absorption rate of carbohydrates, decreases insulin demand and thus controls blood sugar levels. Previous work by Hassan and Mohieldein[19] also recognized the antihyperglycemic potential of aqueous date seed extract when given to diabetic rats in an 8 weeks research. This effect may be ascribed to aggravated insulin secretion by beta cells.

A most rigorous microvascular complication of diabetes mellitus is nephropathy and researchers have reported that intensifying proteinuria causes the continuing decline of renal function indexes which is the most important risk factor for accelerated renal injury.[20]

Treatment with Ajwa seed diet significantly ameliorated the renal functions parameters for renal damage in serum including creatinine, urea and microalbuminuria and increased the urinary creatinine and creatinine clearance levels in urine proposing that Ajwa date seed ingestion may decrease diabetes instigated renal injury.

Results of present study are yet again in agreement to a research by Abdelaziz[12] in which the researchers demonstrated that date seed suspension (Hayani) has improved renal biochemical markers in serum and urine in 4 weeks time period in diabetic rats demonstrating that recovered metabolic control that achieves normoglycemia can extensively decrease development and succession of diabetic nephropathy.

Diabetes mellitus is characterized by increased oxidative stress in all tissues. In oxidative stress, there is an emergence of free radicals in the body that damage all tissues through enhancing lipid peroxidation. Insulin resistance is also increased through the enhancement of proinflammatory cytokines, metabolic processes and reduction in defensive enzymes of the body. [21]

A growing number of studies have demonstrated that P dactylefera contains a large quantity of antioxidants. Date fruits and seeds both are a good source of antioxidants, phytochemicals like minerals, flavonoids and excellently absorbable polyphenols. P.dactylefera seeds had shown elevation of anti-oxidative enzymes like glutathione S-transferase, catalase, superoxide dismutase in kidneys suffering from diabetic stress by declining glycation of these enzymes and free reactive radical scavenging activity.[22]

Formerly published data found that maximum polyphenolic content was found in the Ajwa date. Roasted pit powder of Ajwa date contains total phenols & total flavonoids in the quantity of 1204. 7mg and 530 mg per 100g respectively. Ajwa date seed has the utmost amount of flavonoids including rutin, catechin & quercitin (13.7mg per kg).[9] Antidiabetic potential of rutin through inhibition of glycolytic enzymes has been proved already.[23]

Within the body, polyphenols being reducing

agents suppress reactive free radical species, inhibit lipid peroxidation and slow down the diminution of protecting antioxidant enzymes in severe oxidative stress. Ajwa showed the highest (96.3%) DPPH scavenging activity when compared to other varieties and polyphenols and flavonoids are considered to play the main role as an antioxidant.[24]

Powerful antioxidant effects of dates especially Ajwa, have been explored in a few studies. Arshad 25 reported that Ajwa seed extract has 74µg/ml of gallic acid equivalents and good radical scavenging activity in DPPH (85%), lipid peroxidation (71.1%) ABTS (27%) assays and elevated essential antioxidant enzymes including superoxide dismutase, carnitine acetyltransferase.

In the light of that, our findings concerning the protective effects of Ajwa seed and fruit against the diabetic microvascular complications may be accredited to the occurrence of the aforesaid antioxidant phytoelement.

CONCLUSION

This study reports that Ajwa date seed (Phoenix dactylefera) possesses significant anti-hyperglycemic and nephroprotective activity in alloxanized diabetic nephropathic rats. The results showed that Ajwa seed appreciably ameliorated blood glucose levels, serum urea, serum creatinine, microalbuminuria levels and improved growth as well as urine creatinine and creatinine clearance levels. Ajwa fruit has shown a lesser effect. More studies are needed for the detection and segregation of active phytoconstituents responsible for the nephroprotective effect.

Conflict of Interest

The authors declare no conflict of interests

Acknowledgement

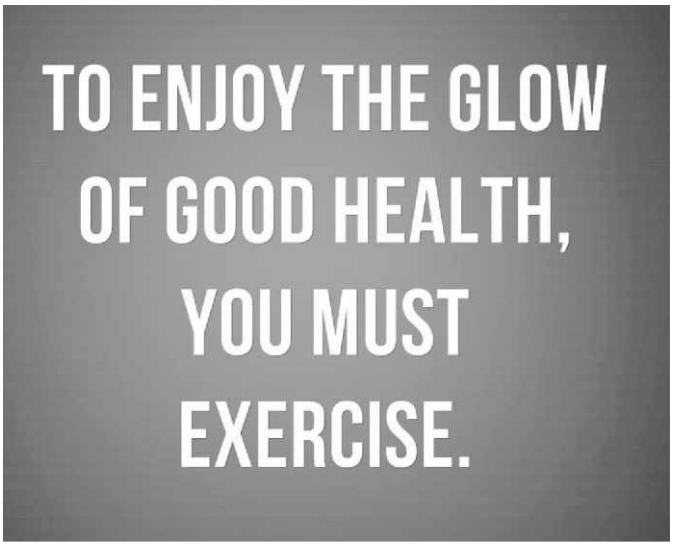
We are sincerely thankful to the staff of animal house and experimental laboratory Pharmacology of Post Graduate Medical Institute, Lahore, Pakistan, for providing research facilities and technical support for the current study.

REFERENCES

1. Cho NH, Shaw JE, Karuranga S, Huang Y, Rocha JD, Ohlrogge AW, et al. IDF Diabetes Atlas : Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018;138:271–81.
2. Hills AP, Arena R, Khunti K, Yajnik CS, Jayawardena R, Henry CJ, Street SJ, Soares MJ MA. Epidemiology and determinants of type 2 diabetes in south Asia. Lancet Diabetes Endocrinol. 2018;
3. Ullah A. Diabetes mellitus and oxidative stress — A concise review. Saudi Pharm J. 2016;24(5):547–53.
4. Rohilla A, Ali S. Alloxan Induced Diabetes : Mechanisms and Effects. Int Res Pharm Biomed Sci. 2012; 3(2):819–23.
5. Verma S, Gupta M, Popli H, Aggarwal G. Diabetes mellitus treatment using herbal drugs. Int J Phytomedicine. 2018;10(1):01.
6. Zhang CR, Aldosari SA, Vidyasagar PSPV, Shukla P, Nair MG. Health-benefits of date fruits produced in Saudi Arabia based on in vitro antioxidant, anti-inflammatory and human tumor cell proliferation inhibitory assays. J Saudi Soc Agric Sci. 2017; 16(3): 287–93.
7. Khalid S, Ahmad A, Masud T, Asad MJ, Sandhu M. Nutritional assessment of ajwa date flesh and pits in comparison to local varieties. J Anim Plant Sci. 2016;26(4):1072–80.
8. Khalid S, Khalid N, Khan RS, Ahmed H, Ahmad A. A review on chemistry and pharmacology of Ajwa date fruit and pit. Trends Food Sci Technol. 2017; 63:60–9.
9. Ahmed A, Arshad MU, Saeed F, Ahmed RS, Chatha SAS. Nutritional probing and HPLC profiling of roasted date pit powder. Pakistan J Nutr. 2016; 15(3): 229–37.
10. Eid N, Enani S, Walton G, Corona G, Costabile A, Gibson G, et al. The impact of date palm fruits and their component polyphenols, on gut microbial ecology, bacterial metabolites and colon cancer cell proliferation. J Nutr Sci. 2014;3(22):46.
11. Sarfraz M, Khaliq T, Khan JA, Aslam B. Effect of aqueous extract of black pepper and ajwa seed on liver enzymes in alloxan-induced diabetic Wister albino rats. Saudi Pharm J [Internet]. 2017; 25(4): 449–52.
12. Abdelaziz DHA, Ali SA, Mostafa MMA. Phoenix dactylifera seeds ameliorate early diabetic complications in streptozotocin-induced diabetic rats. Pharm Biol. 2015;53(6):792–9.
13. Ali A, Abdu S. Antioxidant Protection against

Pathological Mycotoxins Alterations on Proximal Tubules in Rat Kidney. 2011;118–34.

14. Imran I, Ather U, Haleema S Butt IM. Amelioration of hyperglycemia by Ajwa date seed and flesh in alloxan induced diabetic rats. JAIMC. 2018; 16(4): 70–4.
15. Imran I, Butt IM, Naqvi F, Mansoor M. Antidiabetic and Antinephropathic Potential of Ajwa Pit and Pulp (Phoenix dactylefera) in Alloxanized Diabetic Rats. Proc SZMC. 2020;34(1):39–43.
16. Ahmad M, Zafar M, Sultana S. Fruit Plant Species Mentioned in the Holy Qura' n and Ahadith and Their Ethnomedicinal Importance Faculty of Pharmacy Gomal University, Dera Ismail Khan, Pakistan. Ethnomedical Study. 2009;5(2):284–95.
17. Garnham A, Wong C, Levinger P, Asrar M. of Inflammatory Pathways, Physical Activity and Exercise. Exerc Immunol Rev. 2017;94–109.
18. Ahmed S, Khan RA, Jamil S, Afroz S. Antidiabetic effects of Native date fruit Aseel (Phoenix dactylifera L.) in normal and hyperglycemic rats. Pak J Pharm Sci. 2017;30(5):1797–802.
19. Hasan M, Mohieldein A. In vivo evaluation of anti diabetic, hypolipidemic, antioxidative activities of saudi date seed extract on streptozotocin induced diabetic rats. J Clin Diagnostic Res. 2016;10(3):06-12.
20. Gluhovschi C, Gluhovschi G, Petrica L, Timar R, Velciov S, Ionita I, et al. Urinary Biomarkers in the Assessment of Early Diabetic Nephropathy. J Diabetes Res. 2016;2016:1–13.
21. Volpe CMO, Villar-Delfino PH, Dos Anjos PMF, Nogueira-Machado JA. Cellular death, reactive oxygen species (ROS) and diabetic complications review-Article. Cell Death Dis. 2018;9(2).
22. Habib HM, Platat C, Meudec E, Cheynier V, Ibrahim WH. Polyphenolic compounds in date fruit seed (Phoenix dactylifera): Characterisation and quantification by using UPLC-DAD-ESI-MS. J Sci Food Agric. 2014;94(6):1084–9.
23. Dubey S, Ganeshpurkar A, Ganeshpurkar A, Bansal D, Dubey N. Glycolytic enzyme inhibitory and antiglycation potential of rutin. Futur J Pharm Sci. 2017; 3(2):158–62.
24. Khalid S, Ahmad A, Kaleem M. Antioxidant activity and phenolic contents of Ajwa date and their effect on lipo-protein profile. 2017;7(6):396–410.
25. Arshad FK, Haroon R, Jelani S, Masood H Bin. A Relative in Vitro Evaluation of Antioxidant Potential Profile of extracts from Pits of Phoenix dactylifera L. (Ajwa and Zahedi Dates). Int J Adv Inf Sci Technol. 2015;35(35):1–11



THREE DELAYS IN CRITICAL OBSTETRIC PATIENT

Safia Parveen,[1] Mahpara Shaukat,[2] Hina Ilyas,[3] Zareen Amjad,[4] Khadim Hussain,[5] Hina Nabi[6]

How to cite: Parveen S, Shaukat M, Ilyas H, Amjad Z, Hussain K, Nabi H. Three delays in critical obstetric patients. JAIMC. 2021; 19(1): 185-189.

Abstract

Background: Pregnancy places the maternal life at risk in various aspects. Maternal mortality rate is significantly higher in the developing countries. Lack of health care facilities, social and economical factors including education, nutrition and distance from medical help remains the main contributory factors for high mortality.

Objective: To identify the impact of three obstetric delays on outcome of critically ill patients presenting in DHQ teaching hospital Sahiwal.

Methodology: This was an observational study conducted at department of Obstetrics and Gynecology, Sahiwal Medical College teaching hospital Sahiwal from June 2016 to March 2019. Fifty critically ill patients were identified. Data was entered in pre- designed proforma.

Results: Mean age of the patient and husband was 28.70 + 5.81 and 35.72 + 5.8 yrs respectively. Husbands were more educated compared to their wives (Fig 1). Delay in recognizing deteriorating condition and decision to seek medical care was the most prominent form of obstetric delay. Initial management of the patients was given by senior doctors in 62% of the cases, followed by WMO (20%) and nurses (18%). Mortality was observed in 6 cases while complications were reported in 30 cases.

Conclusion: The most common delay observed in the present study was delay in recognizing patient's condition and seek appropriate treatment. So there is dire need to improve literacy rate and healthcare education regarding pregnancy and its complications to reduce the incidence of first delay.

Key Words: Poor socioeconomic status, Low literacy rate, In appropriate health seeking behavior, Lack of healthcare facilities, Transportation problems, Obstetrical care

Every year a number of women die due to pregnancy or pregnancy related complications. According to an estimate made by UN Maternal Mortality Estimation Inter-Agency Group, 303,000 maternal deaths occurred in 2015. The death rate was as low as 12 deaths per 100000 live births in high-income countries to as high as 546 deaths per 100000 live births in sub-Saharan Africa.[1] Most of these deaths are attributable to delay in access to quality healthcare services and initiation of timely and adequate management.[2] The delays largely depends on various factors including socio-economic status, literacy rate, availability of service providers & medical facilities and health seeking behavior of the individuals.[3]

Delay in access to quality health services in critical obstetric patients is major determinant of maternal morbidity and mortality.[4] Three delays are commonly encountered in obstetric patients which are defined in chronological order. These include (i) understanding the severity of the problem and decision making at home to access healthcare services (ii) transportation to medical facility and (iii) delay in initiation of treatment at health center.[5] In a study, overall delay was identified in 54% of the obstetric cases. At least one of the delay was present in cases with maternal deaths, 68% in cases of near miss

1. Safia Parveen
2. Mahpara Shaukat
3. Hina Ilyas
4. Zareen Amjad
5. Khadim Hussain
6. Hina Nabi

1-4,6. Sahiwal Medical College
5. NMU, Multan

Correspondence:
Dr. Safia Parveen, *Professor of Obstetrics &Gynecology Sahiwal Medical College, E- mail: drsaafia@hotmail.com*

Submission Date: 16-10-2020
1st Revision Date: 15-11-2020
Acceptance Date: 19-11-2020

events and 52% in cases presenting with potentially life threatening conditions.[6]

Studies have associated inappropriate health seeking behavior with worse health outcome. Inappropriate health seeking behavior is the major contributor of first obstetric delay and is six times more common in poorest quartile of the society compared to richest quartile.[7] Researchers identified recognition of seriousness of the illness in 67.3% of the cases, affordability in 9.1%, geographical accessibility to health services in 4.6% and quality of services in 6.8% of the cases of inappropriate health seeking behavior.[8] Another study reported availability of primary healthcare services at a reasonable distance was positively associated with deliveries at health centers and was common in urban areas compared to rural areas.[9]

In a recent study from Islamabad, Pakistan recognized poverty, maternal education and lack of community based health promotion programs as key factors for poor health statistics.[10] Significant numbers of women die even after reaching at hospital in time. According to census data of the Mozambique, 46% of the deaths occurred within health facilities.[2] Knight and his colleagues identified a list of thirty-two different variables which were associated with third-delay in obstetric care. They categorized these items into 6 major groups including lack of appropriate training or skills, non-availability of medicines, shortage of doctors and nurses, improper equipment, low staff motivation due to over-load and no standard policy guidelines in decreasing order.[11]

Lowering maternal, neonatal and infant mortality rate to an acceptable level is the target for Millennium Development Goal (MDG) as laid by United Nations.[12] Despite much improvement in healthcare system delivery and accessibility to health services, maternal, neonatal and infant mortality rates are still very high in Pakistan. According to the recent data of United Nations International Children's Emergency Fund (UNICEF)maternal mortality rate is 178 with every 100,000 live births, neonatal mortality rate is 46 per 1000 live births and under-five mortality rate is81 per 1000 live births in Pakistan.[13]

Pakistan is a developing country and a large number of people live below poverty-line and are vulnerable to in-appropriate health seeking behavior. A significant number of women die due to lack of accessibility to quality health services. Keeping in view the poor-socioeconomic status and low literacy rate in district Sahiwal, the current study is planned to identify the impact of three obstetric delays on outcome of critically ill patients presenting in DHQ teaching hospital Sahiwal.

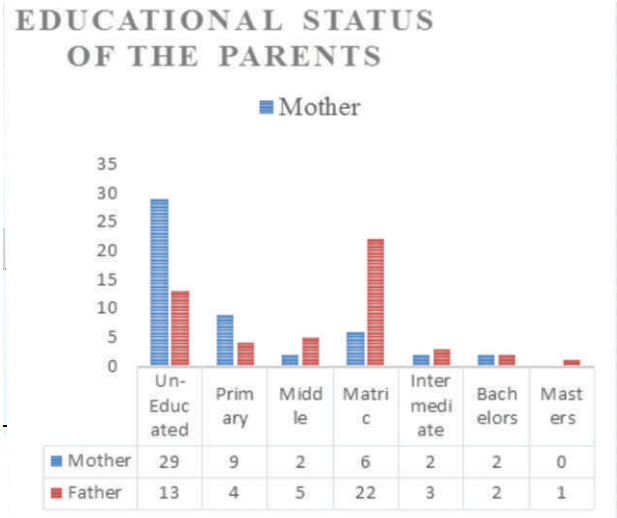
METHODOLOGY

This was an observational study conducted at department of Obstetrics and Gynecology, DHQ teaching hospital Sahiwal from June 2016 to March 2019. The approval of the study protocol was obtained from institutional ethical board. During the study period, 50 critically ill patients presenting in the gynae emergency room were identified. Demographic information, information regarding maternal and father education, profession and monthly income was noted. Obstetric history, antenatal care and data regarding recognition of seriousness of the issue, transportation to the health facility and time and nature of treatment at hospital was obtained and noted in a pre-designed pro forma. The patients were then followed till the discharge from the hospital or death.

RESULTS

A total of 50 females presenting to emergency department and labor room were included in the study. Mean age of the patient and husband was 28.70 + 5.81 and 35.72 + 5.8 yrs respectively (Table 1). Husbands were more educated compared to their wives (Fig 1). Delay in recognizing deteriorating condition and decision to seek medical care was the most prominent form of obstetric delay (table 2).Three patient presenting with prolonged delay were excluded from the analysis of the first delay as they could severely affect its values. One of the

patient presented with peritonitis after lapse of 360 hours. The other one presented with ruptured ectopic after 37 hours and 3rd with ruptured uterus after 21 hours. In 1st and 3rd cases, both parents were illiterate while in 2nd case both were educated. Initial management of the patients was given by senior doctors in 62% of the cases, followed by WMO (20%) and nurses (18%). Mortality was observed in 6 cases while complications were reported in 30 cases (Table 3).



DISCUSSION

Maternal mortality rate is direct indicator of type and quality of healthcare services in an area and is affected by numerous modifiable and non-modifiable risk factors. Some of the common factors include multiparity, lack of health education and family planning, illiteracy, poor socio-economic conditions and dearth of health care facilitates in rural areas.[14] The Obstetric delay which lead to complications are majorly categorized into three types. The first delay is due to inability to recognize deteriorating condition of the patient, fear of hospital and cost incurred on treatment and lack of ability & availability of decision makers especially in working class. Once the decision to seek medical care is made, a 2nd delay is encountered during transportation to the facility. A third delay is often observed due to pre-payment policies in private hospitals, waiting for laboratory reports and waiting time before preparation of the operation e.g. equipment, blood, operation theater and availability of senior / skilled doctors.[15]

Table 2: Obstetric Delay

Obstetric Delay		Time
1st Delay	Delay in recognizing patients' condition and decision to seek medical help	4.14 ± 2.92 hour
2nd Delay	Delay in transportation	1.21 ± 0.57 hour
3rd Delay	Initiation of medical treatment	3.0 ± 3.96 min

Table 3: Coplications in Patients

	Frequency	Percentage
Renal Failure	18	36%
DIC	10	20%
Cardiac failure	2	4%
Death	6	12%

The most common delay observed in the present study was delay in recognizing patient condition and seek appropriate treatment. A number of studies have reported lack of antenatal care, delay in identifying risk factors and early referral can decrease incidence of 1st delay.[16] In a study from Odisha, India the 1st and 2nd obstetric delay was observed in 58% of the death cases while 3rd delay was reported in 46.5% of the patients. Most of the women were not having proper ante-natal care similar to the results of our study.[17] The 2nd delay was also observed in most of the cases due to transportation time of the ambulance. Comparable delay was been reported by Bhattacharyya due to non-availability of emergency transport.[18] Another study also reported lack of transportation as the major cause of 2nd delay and associated higher mortality rate.[19]

In the present study, the mean time for 3rd delay was only 3.0 minutes and most of the patients were treated by senior doctors. The results of our study are in contrast with other studies where 3rd delay is reported to be the most prevalent form of delay. The factors associated with 3rd delay include incorrect risk assessment, non-availability of trained staff, shortage of equipment and over load of the patients.[20] Moodley and colleagues reported failure to

follow standard protocols, delay in clinical assessment and responding to abnormalities as pre-determined factors of 3rd delay.[21] Another study concluded that knowledge and skills of health provider for emergency obstetric care can significantly decrease the duration of 3rd delay.[22]

Although socio-economic, geographic, community factors and beliefs can independently affect the length of the delays in obstetric care. However, round-the-clock availability of highly skilled female doctors to deal with obstetric emergencies can significantly decrease the duration of 3rd delay. There is dire need to improve literacy rate and healthcare education regarding pregnancy and its complications to reduce the incidence of first delay while ensuring availability of ambulance services can help reducing time for 2nd delay.

CONCLUSION

The most common delay observed in the present study was delay in recognizing patient's condition and seek appropriate treatment. So there is dire need to improve literacy rate and healthcare education regarding pregnancy and its complications to reduce the incidence of first delay.

REFERENCES

1. Alkema L, Chou D, Hogan D, Zhang S, Moller AB, Gemmill A, et al. Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group. Lancet. 2016;387(10017):462-74.
2. Chavane LA, Bailey P, Loquiha O, Dgedge M, Aerts M, Temmerman M. Maternal death and delays in accessing emergency obstetric care in Mozambique. BMC Pregnancy Childbirth. 2018;18(1):71.
3. Daniel H, Bornstein SS, Kane GC, Health, Public Policy Committee of the American College of P. Addressing Social Determinants to Improve Patient Care and Promote Health Equity: An American College of Physicians Position Paper. Ann Intern Med. 2018;168(8):577-8.
4. Goodman DM, Srofenyoh EK, Olufolabi AJ, Kim SM, Owen MD. The third delay: understanding waiting time for obstetric referrals at a large regional hospital in Ghana. BMC Pregnancy and Childbirth. 2017;17(1):216.
5. Calvello EJ, Skog AP, Tenner AG, Wallis LA. Applying the lessons of maternal mortality reduction to global emergency health. Bull World Health Organ. 2015;93(6):417-23.
6. Pacagnella RC, Cecatti JG, Parpinelli MA, Sousa MH, Haddad SM, Costa ML, et al. Delays in receiving obstetric care and poor maternal outcomes: results from a national multicentre cross-sectional study. BMC Pregnancy Childbirth. 2014;14:159.
7. Latunji OO, Akinyemi OO. Factors Influencing Health-Seeking Behaviour among Civil Servants in Ibadan, Nigeria. Ann Ib Postgrad Med. 2018; 16(1): 52-60.
8. Onwujekwe O, Onoka C, Uzochukwu B, Hanson K. Constraints to universal coverage: inequities in health service use and expenditures for different health conditions and providers. Int J Equity Health. 2011; 10:50.
9. Ng'anjo Phiri S, Kiserud T, Kvale G, Byskov J, Evjen-Olsen B, Michelo C, et al. Factors associated with health facility childbirth in districts of Kenya, Tanzania and Zambia: a population based survey. BMC Pregnancy Childbirth. 2014;14:219.
10. Rehman A, Shaikh BT, Ronis KA. Health care seeking patterns and out of pocket payments for children under five years of age living in Katchi Abadis (slums), in Islamabad, Pakistan. Int J Equity Health. 2014;13:30.
11. Knight HE, Self A, Kennedy SH. Why are women dying when they reach hospital on time? A systematic review of the 'third delay'. PLoS One. 2013; 8(5): e63846.
12. United Nations. United Nations Development Programme: MDG Acceleration Framework. 2011 [cited 2019 12 Jul]. Available from: https://www.undp.org/content/dam/undp/library/MDG/MDG%20Acceleration%20Framework/MAF%20brochure%20web-en.pdf.
13. United Nations International Children's Emergency Fund. Maternal and Newborn Health Disparities, Paksitan 2015 [cited 2019 12 Jul]. Available from: https://data.unicef.org/wp-content/uploads/ country_profiles/Pakistan/country%20profile_PAK.pdf.
14. MacDonald T, Jackson S, Charles M-C, Periel M, Jean-Baptiste M-V, Salomon A, et al. The fourth delay and community-driven solutions to reduce maternal mortality in rural Haiti: a community-based action research study. BMC Pregnancy and Childbirth. 2018;18(1):254.

15. Thaddeus S, Maine D. Too far to walk: Maternal mortality in context. Social Science & Medicine. 1994;38(8):1091-110.
16. Khandale SN, Kedar K. Analysis of maternal mortality: a retrospective study at tertiary care centre. 2017. 2017;6(4):4.
17. Paul B, Mohapatra B, Kar K. Maternal Deaths in a Tertiary Health Care Centre of Odisha: An In-depth Study Supplemented by Verbal Autopsy. Indian J Community Med. 2011;36(3):213-6.
18. Bhattacharyya S, Issac A, Rajbangshi P, Srivastava A, Avan BI. "Neither we are satisfied nor they"-users and provider's perspective: a qualitative study of maternity care in secondary level public health facilities, Uttar Pradesh, India. BMC Health Services Research. 2015;15(1):421.
19. Jithesh V, Ravindran TKS. Social and health system factors contributing to maternal deaths in a less developed district of Kerala, India. Journal of Reproductive Health and Medicine. 2016;2(1):26-32.
20. Mgawadere F, Unkels R, Kazembe A, van den Broek N. Factors associated with maternal mortality in Malawi: application of the three delays model. BMC Pregnancy and Childbirth. 2017;17(1):219.
21. Moodley J. Maternal deaths associated with eclampsia in South Africa: Lessons to learn from the confidential enquiries into maternal deaths, 2005 - 2007. S Afr Med J. 2010;100(11):717-9.
22. Ameh CA, Kerr R, Madaj B, Mdegela M, Kana T, Jones S, et al. Knowledge and Skills of Healthcare Providers in Sub-Saharan Africa and Asia before and after Competency-Based Training in Emergency Obstetric and Early Newborn Care. PLoS One. 2016;11(12):e0167270.

KNOWLEDGE, ATTITUDE AND PRACTICE OF MOTHERS REGARDING ZINC SUPPLEMENTS IN DIARRHEAL PATIENTS UNDER FIVE YEARS OF AGE

Ayesha Rehman,[1] Namra Nazir,[2] Muhammad Naqash,[3] Rizwan Gohar,[4] Agha Shabbir Ali[5]

How to cite: Rehman A, Nazir N, Naqash M, Gohar R, Ali AS. Knowledge, attitude and practice of mothers regarding zinc supplements in diarrheal patients under five years of age. JAIMC. 2021; 19(1): 190-194.

Abstract

Background: Diarrhea is a global disease affecting people of all ages but causes high rate of mortality and morbidity in children of under 5 years of age especially in developing countries like Pakistan. According to world bank collection of development indicators, in Pakistan prevalence of diarrhea (percentage under 5 years of age) was 23.7%.

Objective: To determine knowledge, attitude and practice of mothers regarding zinc supplementation in diarrheal patients under 5 years of age.

Methodology: A cross-sectional study was conducted in pediatrics out-patient department of Lahore General Hospital Lahore from April 2019 to July 2019. We conducted a survey-based study on a group of 100 mothers to elicit information about knowledge, attitude and practice of mothers regarding zinc supplements in acute diarrhea in children under 5 years of age.

Results: A total 100 mothers were enrolled in the study. Of these,9% belonged to rural area and 91% were from urban areas. 35% were uneducated and 65% educated. 82% were housewives while 18% were working ladies, out of which 9% belongs to health setup. 34% of mothers had the knowledge about zinc supplement and also practiced it while 66% had no knowledge regarding zinc and hadn't practiced zinc either.

Conclusion: By applying chi-square test, results showed that there was no significant relationship between education of mothers and the knowledge, attitude and practice of zinc supplementation. In addition to domestic techniques and ORS use, Zinc is one of the major components used for the treatment of diarrheal diseases under 5 years of children but the use of zinc by the mothers is quite low. To make the use of zinc effective and beneficial for children, awareness programs and advertisements can play a major role. These programs can make mothers well aware about the correct use of zinc supplements for the treatment of diarrhea.

K ey Words: Zinc, supplement, diarrhea

Diarrhea is one of the most common causes of morbidity and mortality in children under 5 years of age.[1] As stated by WHO and UNICEF, every year 2 billion cases of diarrheal diseases are reported and 1.9 million children of under 5 years lose their lives due to diarrhea, in developing countries. It can be estimated that on an average >5000 deaths occur each day due to diarrheal infection as after pneumonia, diarrhea is the 2nd leading cause of death worldwide.[2] In under developed countries, every child below 5 years experiences 2-9 episodes of diarrhea each year.[3] From last few decades, due to betterments in the ORS techniques and reforms in sanitary and hygienic measures, the death rate due to diarrhea has decreased tremendously from 5 million annually to 1.5 million deaths in 2004 but diarrhea still prevails at the same rate.[4]

1. Ayesha Rehman
2. Namra Nazir
3. Muhammad Naqash
4. Rizwan Gohar
5. Agha Shabbir Ali

1-3. Ameer-ud-Din Medical College, Lahore
4,5. *Pediatrics Department, Lahore General Hospital*

Correspondence:
Dr. Rizwan Gohar,Assistant Professor Pediatrics, *LGH, Ameer-ud-Din Medical College, Lahore*

Submission Date: 08-11-2020
1st Revision Date: 07-12-2020
Acceptance Date: 11-12-2020

That's why improvements are still needed for declining this high rate of incidence of diarrhea.

Oral rehydration salts play an important role in the treatment of dehydrating diarrhea, resulting in reduced mortality but don't decrease the duration of episodes or their consequences, such as malnutrition. From the last few years, along with ORS zinc has become a necessary adjunct for the treatment of diarrhea in children under 5 years of age. Zinc is an essential trace element and 2nd most abundant metal in humans after iron. It is required for the proper functioning of approx. more than 300 enzymes and 1000 transcription factors and cell growth.[5] Zinc is necessary for better absorption of water and electrolytes by intestine.

It maintains healthy immune system of human body specially by removal of pathogens from the gut during diarrheal episode. According to the U.S. Institute of Medicine (IOM) updated Estimated Average Requirements (EARs) and Recommended Dietary Allowances (RDAs) for zinc for infants up to 12 months is 3 mg/day. For children ages 1–13 years the RDA increases with age from 3 to 8 mg/day. Zinc deficiency causes depressed growth, diarrhea, impotence and delayed sexual maturation, alopecia, eye and skin lesions, impaired appetite, altered cognition, impaired immune functions, defects in carbohydrate utilization, and reproductive teratogenesis. Zinc deficiency depresses immunity, but excessive zinc does also. Zinc deficiency is the important cause of diarrhea in children under 5 year of age with high mortality rate. Recent studies have shown that zinc when used along with low osmolarity ORS leads to decrease in frequency of acute persistent diarrhea.[6] WHO and UNICEF recommend zinc with ORS in the dose of 20 mg daily for 10-14 days for children and 10 mg per day for infants below six months of age in the treatment for diarrhea[7]. In 2004, The WHO & UNICEF jointly recommended the use of low osmolarity ORS and Zinc supplementation for the control of diarrhea. But the coverage of ORT varies between 2-16% in India.[8] In 2005 zinc has become part of essential drug list for the treatment of diarrhea in the integrated management of childhood illness (IMNCI) and WHO.[9]

As mother is the prime caretaker of a child, so mother's knowledge plays an important role in the treatment of diarrheal episodes. Proper knowledge of treatment, awareness regarding use of zinc supplements and other techniques and practice of previous and new therapy for the diarrheal management are important steps taken by mother for the complete recovery from acute diarrhea. Lack of mother's knowledge and awareness about diarrheal management techniques leads to improper use of treatment strategies[10]. This study is based on the evaluation of knowledge, attitude and practices of mothers regarding zinc supplements in acute diarrhea in children under 5 years of age by assessing their educational level, occupation and source of information.

METHODOLOGY

This study was conducted at pediatrics outpatient department, Lahore General Hospital, Lahore, Pakistan. Mothers of children under five years of age were identified and assessed about their knowledge regarding zinc supplementation in diarrheal infection. It was prospective cross-sectional study aimed to find out the awareness level of mothers about zinc for the treatment of diarrhea, which is a major childhood problem in the developing countries.

This study was carried out from 10th March 2019 – 1st June 2019. Total 100 mothers were engaged over this period and information was obtained. Ethical Approval was taken from the department.

The data was analyzed using statistical package SPSS windows version 25. A p value of less than 0.05 was considered statistically significant. The student t-test was used to compare arithmetic means and parameters while Chi square(X2) test were used to compare categorical data. The bivariate regression analysis was done for different factors.

RESULTS

A total of 100 mothers were enrolled to acess the knowledge, attitude and practice of zinc supple-

ments in chlidren under 5 years of age for treatment of diarrhea. The demographic details are given in table 1.

Out of 100 mothers only 34% had the knowledge about when to give zinc supplementation in case of diarrhea while other 66% do not have the knowledge. Out of these 34, 9 belongs to health setup while other 25 do not belong to health setup.

Table 1: Demographic Details

		Frequency	Percent	Valid Percent	Cumulative Percent
Residence	Rural	9	9	9	9
	Urban	91	91	91	100
	Total	100	100	100	-
Education	Uneducated	35	35	35	35
	uptto 5th grade	15	15	15	50
	upto 8th grade and above	24	24	24	74
	Graduated	26	26	26	100
	Total	100	100	100	-
Occupation	Housewife	82	82	82	82
	working woman	18	18	18	100
	Total	100	100	100	-

Out of 100 mothers 20% had the good, 20% had satisfactory, 2% had poor perception about zinc supplementation while 66% don't know about zinc supplementation. Out of 100 mothers, 32% told that treatment is effective while 2% told that treatment is not effective while 66% had no idea about the treatment.

Out of 100 mothers, 34% had given while 66% had not given zinc supplementation to their child.

Out of 34 mothers who had given Zinc Supplements, 18% had given by herself while 82% had given Zinc Supplements on Doctor's Opinion.

Out of 34 mothers who had given Zinc Supplements, 3% told that the effect appeared after 1 day, 56% told after 1-2 days, 26% told after 2-3 days, 15% told after 3 or more days.

Out of 34 mothers who had given Zinc Supp-lements to the children whenever they suffer from diarrhea, 53% had given zinc supplements after every diarrheal disease, 47% had not given after every diarrheal disease.

Out of 34 mothers who had given Zinc Supplements, 88% had noticed response, 12% had noticed no response.

On application of chi square test, the correlation of knowledge, attitude and practice about zinc therapy with education of mother was found to be non-

Correlation of Knowledge of Zinc Supplements with Education of Mother				
Do you know when to give Zinc Supplements?		Yes	No	Total
Education	Uneducated	10	25	35
	Upto 5th Grade	5	10	15
	Upto 8th Grade & Above	8	16	24
	Graduated	12	14	26
	Total	35	65	100

Correlation of attitude about zinc therapy with education of moth						
What is your perception about Zinc Treatment?		Good	Satisfactory	Poor	Don't Know	Total
Education	Uneducated	4	3	2	26	35
	Upto 5th Grade	1	4	0	10	15
	Upto 8th Grade & Above	5	3	0	16	24
	Graduated	10	2	0	14	26
	Total	20	12	2	66	100

Correlation of Practice of Zinc Supplements with Education of Mother				
Do you know when to give Zinc Supplements?		Yes	No	Total
Education	Uneducated	7	28	35
	Upto 5th Grade	1	14	15
	Upto 8th Grade & Above	7	17	24
	Graduated	9	17	26
	Total	24	76	100

significant. The p value was greater than 0.05.

DISCUSSION

Diarrhea is the major cause of morbidity and mortality in children. According to UNICEF and WHO, in developing countries 2 billion cases of diarrheal cases are reported every year and 1.9 million children of under 5 years died due to diarrhea. According to world bank collection of development indicators, in Pakistan prevalence of diarrhea (% under 5 years of age) was reported to be 23.7% in 2013. In this Study, our aim was to determine the knowledge, attitude and practices of mothers about reduction of Diarrhea by using Zinc Supplements. According to a research in India, only 1.9% mothers had heard of Zinc therapy. UNICEF reported that the knowledge about Zinc therapy in mothers was almost equal to zero.[11] Similarly, low levels of knowledge were reported by Rokkappanavar et al[12], where only 3.8% of mothers gave zinc. Recent studies have been done in Bangladesh and Kenya where rate of zinc awareness and administration was 35% and 32% respectively.[13] According to our study, only 34% of mothers are well aware of zinc supplements and are practicing zinc for the treatment of Diarrhea. A study in India reported that Education levels and Occupation of the mother play significant role in knowledge about Zinc supplements. In contrary to this, in our study there was no association of education and occupation of mothers with awareness about zinc supplements. Even mothers belonging to health professional didn't have significant knowledge about zinc supplementation. Our study has revealed the low knowledge about zinc supplementation in Diarrhea. It emphasized on the need and pointed out the importance of Health education in familiarizing zinc supplementation among mothers because mother plays the most significant role in family care at home. The criteria of our study were hospital based which had a number of limitations. Better sources of information in this regard could be community based and multicentric studies. A case control study can be a better idea for knowing about compliance of zinc therapy because in case control study we can do follow up of patients for a long time to know about merits and demerits of zinc supplementation in diarrheal patients.

CONCLUSION

By applying chi-square test, results showed that there was no significant relationship between education of mothers and the knowledge, attitude and practice of zinc supplementation. In addition to domestic techniques and ORS use, Zinc is one of the major components used for the treatment of diarrheal diseases under 5 years of children but the use of zinc by the mothers is quite low. To make the use of zinc effective and beneficial for children, awareness programs and advertisements can play a major role. These programs can make mothers well aware about the correct use of zinc supplements for the treatment of diarrhea.

REFERENCES

1. Dipak kumar dhar, Niratan Majmuder, Debasish Paul, Assessment of knowledge and practice of mothers of children under five regarding zinc therapy in childhood diarrhea - International journal of advanced and integrated medical sciences, October-December 2016.1;(4): 169-172
2. Journal of Clinical Gastroenterology: January 2013 - Volume 47 - Issue 1 - p 12–20
3. Fischer Walker CL, Perin J, Aryee MJ, Boschi-Pinto C, Black RE. Diarrhea incidence in low- and middle-income countries in 1990 and 2010: a systematic review. BMC Public Health. 2012; 12:220. doi: 1471-2458-12-220.
4. Chiabi A, Monebenimp F, Bogne JB, Takou V, Ndikontar R, Nankap M, Youmba JC, Tchokoteu PF, Obama MT, Tetanye E. Current approach in the management of diarrhea in children: from theory and research to practice and pragmatism. Clin Mother Child Health 2010;7(1):1243-1251.
5. Cherasse Y, Urade Y (November 2017). "Dietary Zinc Acts as a Sleep Modulator". International Jour-nal of Molecular Sciences. 18 (11): 2334. doi: 10.3390/ijms18112334. PMC 5713303. PMID 29113075
6. Bhutta ZA, Black RE, Brown KH, Gardner JM, Gore S, Hidayat A, Khatun F, Martorell R, Ninh NX, Penny ME, Rosado JL, Roy SK, Ruel M, Sazawal S, Shankar A J Pediatr. 1999 Dec; 135(6):689-97.

7. WHO/UNICEF. Clinical management of acute diarrhea Geneva: World Health Organization; 2004. p. 4. (WHO/FCH/CAH/04.07)
8. Jones G, Schultink W, Babille M. Child survival in Indian. Indian journal of pediatrics. 2006; 73(6): 479- 87
9. Clinical management of acute diarrhea: WHO/ UNICEF joint statement Geneva: World Health Organization; 2004
10. Bhatnagar S, Alam S, Gupta P, Management of acute diarrhea: from evidence to policy. Indian pediatrics 2010 Mar 47(3):215-217
11. Management practice of childhood diarrhea in india 2009. UNICEF; 2009 p. 4-7.
12. Rokkappanavar KK, Nigudgi SR, Ghooli S. A study on knowledge and practice of mothers of under 5 children regarding management of diarrhea in urban field practice area of MRMC, Kalaburagi, Karnatka, India. Int J Community Med Public Health 2016; 3(3):705-710.
13. Akhtaruzzaman M, Hossain MA, Khan RH, Karim MR, Choudhury AM, Islma MS, Ahamed F, Khan N, Ahammed SU, Dhar SK, et al. knowledge and Practices of mothers on childhood diarrhea and its management attended at a tertiary hospital in Bangladesh. Mymen singh M ed J 2015 Apr 24 (2): 269-275.

PAP SMEAR VERSUS VISUAL INSPECTION WITH ACETIC ACID (VIA) IN CERVICAL SCREENING PROGRAM

Saira Yunus,[1] Bushra Bano,[2] Hifza Khushnood,[3] Amtullah Zarreen[4]

How to cite: Yunus S, Bano B, Khusnood H, Zareen A. pap smear versus visual inspection with acetic acid (VIA) in cervical screening program. JAIMC. 2021; 19(1): 195-200.

Abstract

Background: Cervical cancer being most prevalent genital tract malignancy among females in developing countries, is depicted by hyperplasia i.e. abnormally increased number of cells and its incubation period is prolonged. It commonly presents in 5th and 6th decade of women's life with pelvic pain, postcoital bleeding, post-menopausal bleeding, vaginal discharge and painful coitus. Cytological interpretation and human papillomavirus (HPV) testing require collection of sample and testing in a laboratory. Colposcopy and Visual inspection with acetic acid (VIA) and Pap smear have been used widely as a tool for the assessment of cervical precancerous lesions. Colposcopy and Pap test being time consuming tool, also need large scale logistics and of course require expertise.

Objective: To determine accuracy of (VIA) visual inspection of cervix after acetic acid application and Pap smear in cervical pre-cancers screening. It was a cross-sectional, non probability sampling for six months from January to July 2019, was done at tertiary care hospital Lahore.

Methodology: Two hundred and sixty five cases, aged 25-65 years with any parity were enrolled and those with diagnosed cervical cancer and history of hysterectomy were excluded at Jinnah hospital Lahore. All basic information was obtained like age, parity and contact details after taking informed consent. The Pap smear sample was taken and fixed with 95% ethanol, 30 minutes before reporting and was labeled. VIA was performed after applying acetic acid (05%) on the cervix with cotton. A naked-eye assessment was done 5 minutes after the application under halogen lamp illuminator. Acetowhite areas were labelled as positive after naked eye assessment. Acetowhite areas were biopsied under anesthesia and sent for histopathology, to identify precancerous lesion or cervical cancer. Results of VIA, Pap smear were compared with histopathology. All data was collected on a proforma. All procedure was done by a single consultant and reporting was done by a single consultant to minimize the bias. Compiled data entered and was analyzed using SPSS 21.

Results: The average female age was 45.30 ± 11.97 years with min and max age as 25 and 65 years. On histopathology 130(49.1%) females had cervical cancer while 129(48.7%) females and 125(47.2%) females had positive findings on VIA and Pap smear. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall diagnostic accuracy of VIA was 93.08%, 94.07%, 93.80%, 93.38% and 93.58% respectively. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall diagnostic accuracy of Pap smear was 88.46%, 92.59%, 92.00%, 89.29% and 90.57% respectively.

Conclusion: The study reflects that the Accuracy of visual inspection of cervix after applying acetic acid (VIA) was found higher and can be used in resource limited settings. Both Pap test and VIA can be combined to detect cervical cancer with high diagnostic accuracy.

Key Words: Cervical carcinoma, cervical screening, histopathology, Pap smear, VIA.

1. Saira Yunus
2. Bushra Bano
3. Hifza Khushnood
4. Amtullah Zarreen

1-4. Department of Gynaecology, Allama Iqbal Medical College, Lahore

Correspondence:
Dr Saira Yunus, *Associate Professor, Department of Gynaecology Jinnah Hospital Lahore*
Email: sairaymian @ gmail.com

Submission Date: 16-11-2020
1st Revision Date: 22-11-2020
2nd Revision Date: 05-12-2020
Acceptance Date: 10-12-2020

Cervical malignancy being the second leading cause of female cancers globally, presents with 527,000 emerging cases anually.[1] cervical precancerous screening should be offered to all females of reproductive age group to detect & prevent cervical cancer at an early stage, which is treatable.[2] cervical screening program if implemented globally, early diagnosis with immediate treatment can give a better chance of survival for this cancer patients. [3,4]

Cervical cytology remains simple non-invasive

and highly effective tool for early diagnosis of precancerous lesions, thus curable and effectively reduces the invasive disease.[3] Both liquid base cytology and Pap test have contributed for significant reduction of cervical malignancy in developed countries.[3] Visual inspection of the cervix with acetic acid is highly sensitive to pick cervical premalignant lesions. VIA is cheap, easy technique and being highly sensitive, carries all salient features for efficacy of any screening projects in developing countries.[4] In local population the prevalence of cervical cancer is detected on VIA is 22%, on Pap smear is 10.8% and on histological diagnosis of CIN/cancer is 58.04% who underwent biopsy.[5]

It was found in a study that VIA had sensitivity of 71.4%, compared to Pap smear which was 78.6%. Similarly specificities were 97.8% and 92.6% respectively. VIA had a Positive predictive value (PPV) of 76.9% and Pap test had 52.4% while negative predictive values (NVP) for each were 97.1% and 97.7% respectively.[6] similar results were shown in another report i.e VIA had sensitivity of 89% (versus pap smear-52%), the specificity of VIA was 87% (versus pap smear-95%). The diagnostic accuracy of both were found 87% and 93% respectively.[7]

A recent local study reported that Sensitivity of VIA was 93.5%, specificity 95.8%, positive predictive value of 76.3%, negative predictive value of 99% and the diagnostic accuracy was 95.6%.[2] Though many local and international studies are done but yet no agreement is made on diagnostic accuracy of VIA and PAP smear test as huge variation exists i.e. for VIA sensitivity ranges from (71.4%-93.5%), and for Pap smear sensitivity ranges from (52% - 95.8%). In developing countries like Pakistan, an efficacious, cheaper alternate tests are required to diagnose the disease at its earliest stage to provide treatment with better outcome and survival. VIA being simplest and easy to understand and perform requires no more logistics and laboratory equipment to deal with. As the results are on the spot on the basis of findings, for all the more reasons VIA is an attractive tool in developing countries like ours. Furthermore, WHO suggested using alternative tools i.e VIA, Pap testing, therefore considering above variable sensitivities in available literature the current study is helpful to add to research.

METHODOLOGY

It was a cross-sectional study, non probability sampling for six months from January to July 2019, was conducted at tertiary care hospital Lahore. 265 cases, aged 25-65 years with any parity were enrolled and thosewith diagnosed cervical cancer and history of hysterectomy was excluded at Jinnah hospital Lahore. All basic information was obtained like age, parity and contact details after taking informed consent.The Pap smear sample was taken and fixed with 95% ethanol, 30 minutes before

Table 1: *: Distribution of Cases with Respect to Age, Parity and Duration of Symptoms*

Age	25-40 years	129	48.68%
	41-65 years	136	51.32%
Parity	< 4	135	50.94%
	4 or > 4	134	49.06%
Duration of symptoms	< 4 weeks	143	53.96%
	>4 weeks	122	46.04%

Table 2: *Comparison between Findings of VIA and Histopathology*

		On histopathology		Total
		Positive	Negative	
VIA	**Positive**	121	8	129
	Negative	9	127	136
Total		130	135	265

Sensitivity=93.08% , Specificity=94.07%
Positive predictive value=93.08%
Negative predictive value=93.38%
Diagnostic accuracy=93.58%
Chi-square = 2.013, P-value = <0.001*

Table 3: *Comparison between Findings of Pap Smear and Histopathology*

		On histopathology		Total
		Positive	Negative	
Pap smear	**Positive**	115	10	125
	Negative	15	125	140
Total		130	135	265

Sensitivity=88.46% Specificity=92.59%
Positive predictive value=92.00
Negative predictive value=89.29%
Diagnostic accuracy=90.57%
Chi-square = 1.746, P-value = <0.001*

Table 4: *Comparison between Findings of VIA & Histopathology with Respect to Age Groups, Parity & Duration of Symptoms*

Variables	Range	VIA	On H/P		P - Value	Sensitivity %	Specificity %	PPV %	NPV %	Diagnostic Accuracy %
			Positive	Negative						
Age Group	24-40 Years	Positive	57	04	<0.001*	87.18	94.37	93.44	89.33	91.18
		Negative	08	67						
	41-65 Years	Positive	64	04	<0.001*	98.46	93.75	94.12	98.36	96.12
		Negative	01	60						
Parity	< 4	Positive	69	04	<0.001*	92.00	93.33	94.52	90.32	92.59
		Negative	06	56						
	⩾ 4	Positive	52	04	<0.001*	94.55	94.67	92.86	95.95	94.62
		Negative	03	71						
Duration of Symptoms	< 4 Weeks	Positive	80	04	<0.001*	90.91	92.73	95.24	86.44	91.61
		Negative	08	51						
	⩾ 4 Weeks	Positive	41	04	<0.001*	97.62	95.00	91.11	98.70	95.90
		Negative	01	76						

Table 5: *Comparison between Findings of Pap-Smear & Histopathology with Respect to Age Groups, Parity & Duration of Symptom*

Variables	Range	Pap smear	On H/P		P - Value	Sensitivity %	Specificity %	PPV %	NPV %	Diagnostic Accuracy %
			Positive	Negative						
Age Group	24-40 Years	Positive	58	04	<0.001*	89.23	94.37	93.55	90.54	91.91
		Negative	07	67						
	41-65 Years	Positive	57	06	<0.001*	87.69	90.62	90.48	87.88	89.15
		Negative	08	58						
Parity	< 4	Positive	62	06	<0.001*	82.67	90.00	91.18	80.60	85.93
		Negative	13	54						
	⩾ 4	Positive	53	04	<0.001*	96.36	94.67	92.98	97.26	95.38
		Negative	02	71						
Duration of Symptoms	< 4 Weeks	Positive	84	06	<0.001*	95.45	89.09	93.33	92.45	93.01
		Negative	04	49						
	⩾ 4 Weeks	Positive	31	04	<0.001*	73.81	95.00	88.57	87.36	87.70
		Negative	11	76						

reporting and waslabeled. VIA was performed after applying acetic acid (05%) on the cervix with cotton. A naked-eye assessment was done 5 minutes after the application under halogen lamp illuminator. Acetowhite areas were labelled as positive after naked eye assessment.Acetowhite areas were biopsiedunder anesthesia and sent for histopathology, to identify precancerous lesion or cervical cancer. Results of VIA, Pap smear were compared with histopathology. All data was collected on a proforma. All procedure was done by a single consultant and reporting was done by a single consultant to minimize the bias. Compiled data entered and was analyzed using SPSS 21. Qualitative data such parity, findings on histopathology (positive and negative), VIA and Pap smear were presented as frequencies and percentages. Quantitative data such as age and paritywas presented to calculate diagnostic accuracy (sensitivity, specificity, PPV and NPV, diagnostic accuracy) of VIA and Pap smear and compared with histopathology. Data stratification was done to address effect modifiers. After stratification Chi-square test was applied and significant P-value was labelled as <0.05.

RESULTS

The mean age of all females was 45.30 ± 11.97 years with minimum and maximum age as 25 and 65 years. There were 136(51.3%) females who were 25-40 years old and 129(48.7%) females were 41-65 years old. There were 135 (50.9%) females who had parity < 4 and 130 (49.1%) females had parity ≥4. There were 143(54%) females who had duration of symptoms since < 4 weeks and 122 (46%) of the cases had duration of symptoms since ≥ 4 weeks. Table 1

On histopathology 130 (49.1%) females had cervical cancer while 129 (48.7%) females and 125 (47.2%) females had cervical cancer on VIA and Pap smear.

There were 121 females who positive findings on both histopathology and VIA, 127 females had negative findings on both histopathology and VIA, there were 8 false positive and 9 were false negative. The sensitivity, specificity, posi-tive predictive value (PPV), negative predictive value (NPV) and overall diagnostic accuracy of VIA was 93.08%, 94.07%, 93.80%, 93.38% and 93.58% respectively. On applying Chi-square test the p-value was also significant, showing that there was significant association between findings of histopathology and VIA, p-value < 0.001. Table -2

There were 115 females who had positive fin-dings on both histopathology and Pap smear, 125 females had negative findings on both histo-pathology and Pap smear. There were 10 false positive and 15 false negative. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall diagnostic accuracy of Pap smear was 88.46%, 92.59%, 92.00%, 89.29% and 90.57% respec-tively. On applying Chi-square test the p-value was also significant, showing that there was significant association between findings of his-topathology and Pap smear, p-value < 0.001. Table -3

On stratifying data for age, parity and duration of symptoms, we found high diagnostic accu-racy for both VIA and pap smear also found significant association between findings of histopathology, VIA and Pap smear, p-value < 0.05. Table -4,5

DISCUSSION

Globally, accounting for 13% of all female cancers in developing countries, cervical malig-nancy is the second in order for all female cancers.[8,9] In Pakistan it is the 5th leading cause of female deaths due to cancers in 15-44 years age group. Unfortunately, the cancer is already in advanced stage by the time patient seeks medical advice.[10] If untreated this deadly cancer, in due course of its time leads to significant weight loss and immunosupp-ression, leading to secondary infections. Hence, early diagnosis at precancerous stage is immensely required by proper screening methods, so that its progression to advanced stage can be prevented.[11]

In developed countries, Pap test and liquid-based cytology is successfully being used to dec-rease cervical cancer. Although they have adopted human papillomavirus (HPV) testing as primary screening tool in population base cervical cancer screen program, cervical cytology still is a basic step in the investigating precancerous lesions. Pakistan being the low resource country, where even the basic necessities are not met with, mainstay screening tool are VIA and the Pap smear testing.[12] HPV test and cervical cytology require collection of sample and reading of test in laboratory settings. In limited settings, the results are available days and weeks after collecting the samples. Contrarily VIA, which is the application of 5% acetic acid to the cervix to detect acetowhite areas with lesion identification immediately during the procedure.[13] Colposcopy and Pap testing require an extensive logistics, personnel expertise, along with time contstraints.[14] A recent local study reported that Sensitivity of 93.5%, speci-ficity 95.8%, positive predictive value 76.3%, nega-tive predictive value 99% and diagnostic accuracy was 95.6%.2 In our study the sensitivity of 88.46%, specificity 92.59%, positive predictive value 92.00 %, negative predictive value 89.29% and diagnostic accuracy of Pap smear was 90.57%. We found high diagnostic accuracy of VIA in current study.

In 2012, a study showed, 23 out of 300 women screened had aceto-white changes on VIA. Pap test showed 14 women out of the 300 had ASCUS or worse lesions, 11 had positive lesions on both VIA and cytology, 12 had positive findings on VIA only, and 3 had positive only cytological changes. Conclusively, VIA was found more sensitive (94.44%) than Pap smear (55.55%). However, VIA had slightly lower specificity (97.87%) than cytology (98.58%). The PPV was 73.91% for VIA and 71.42 % for Pap test15 but in our study sensitivity 93.08% and specificity 94.07% both were high for VIA than Pap test.

Another study at Vietnam was aimed to ascertain the diagnostic accuracy of VIA and cytology in a cervical cancer screening program at community level. The sensitivity 88.8%, specificity 43.8%, accuracy 63.4%,PPV 51.2% and NPV83.3% of VIA for CIN2+ were labelled. Pap smear showed sensitivity 58.0%, specificity 85.2%,PPV 69.9%, NPV 83.3% and Diagnostic accuracy of 61.3%. VIA showed high sensitivity but with limited accuracy in diagnosis of pre-cancerous lesions in cervical cancer screening. The Pap test has acceptable sensitivity and specificity, but it has high false-negative rates.[16] Sinha et al, reported that VIA had sensitivity of 93.3% and the Pap test had 93.8% showing nearly equal results. The Pap test had more specificity than VIA, i.e. 72.9 vs 60% respectively, contrarily in our study VIA was found to have more sensitivity & specificity. Diagnostic accuracy for Pap test was found 77.3% and for VIA it was 66.7% which was in our study 93.58% and 90.57% respectively[17].

In 2015, a local study by Khan et al, showed diagnostic accuracy of VIA as 95.6%[2]. Bano et al showed the sensitivity of 71.4% for VIA and for Pap smear it was 78.6%. Specificities were 97.8% for VIA and 92.6% for Pap test correspondingly. PPV was 76.9% for VIA and 52.4% was for Pap test, while NPV was 97.1% for VIA and 97.7% for Pap test respectively, thus showing comparable sensitivity and specificity of VIA and Pap smear. Low cost, easy applicability and immediate results make VIA a useful screening test in developing countries like Pakistan6. In 2013, another local study revealed that of 519 cases, 70 were screened positive and 29 were histologically proven for cervical intraepithelial neoplasia. Of these, 26 were positive on visual inspection, 14 on cytology; and 30 on both combined test. The sensitivity of visual inspection was 78.5% and for Pap test it was 61.1 %($P < 0.001$). The specificity of visual inspection was 99.3% and for cytology it was 99.4% ($P< 0.1$). Combined test with more predictive accuracy may be used for opportunistic screening.[18]

Moreover, requirements for doing a pap test is a speculum, spatula, lamp, cytobrush, microscope and a pathologist along with a 2 weeks interval time until follow up visit. Contrary for doing VIA any trained personnel nurse, doctor, who can use a speculum can easily perform the test.VIA seems to be useful as it is an easy way for a novice, and all the more does not require extensive logistics. VIA is simple inexpensive test, which can even be performed by paramedics after short training course for procedure and interpretation.[19]

CONCLUSION

VIA is a cheap and effective tool for cervical screening with higher diagnostic accuracy compared to Pap smear. Therefore in low resource settings it seems to be a useful technique to incorporate in screening programme as even for beginners it is easy to understand and needs minimal time to carry out and label the findings without requiring extensive logistics and laboratory facilities. It is further emphasized that both VIA and Pap test can be combined to get further accuracy.

REFERENCES

1. Williams D, Davies M, Fiander A, Farewell D, Hillier S, Brain K. Women's perspectives on human papillomavirus self-sampling in the context of the UK cervical screening program. Health Expectations. 2017: DOI: 10.1111/hex.12544.
2. Khan M, Sultana SS, Jabeen N, Arain U, Khan S. Visual inspection of cervix with acetic acid: a good alternative to pap smear for cervical cancer scree-

ning in resource-limited setting. J Pak Med Assoc. 2015; 65(2):192-5.

3. Naz U, Naseeb S, Shuja S. Concordance Between Visual Inspection with Acetic Acid Test and Pap Smear in Detection of Cervical Cancer. J Surg Pak (Int). 2016; 21(1):18-22.
4. Shaheen S, Sharma R, Rashi R. Visual Inspection with Acetic Acid (VIA) in cervical cancer screening in low resource settings. Bangladesh J Med Sci. 2014; 13(4):454.
5. Naz U, Hanif S. Agreement between visual inspection with acetic acid and papanicolaou's smear as screening methods for cervical cancer. J Coll Phys Surg Pak. 2014; 24(4):228-31.
6. Bano A, Haq G, Sheikh A. Pap smear versus visual inspection of cervix with acetic acid (VIA) for detection of cervical abnormalities. Pak J Surg. 2013; 29(1):46-51.
7. Bhattacharyya AK, Nath JD, Deka H. Comparative study between Pap smear and visual inspection with acetic acid (via) in screening of CIN and early cervical cancer. J Mid-Life Health. 2015; 6(2):53-8.
8. Jeronimo J, Morales O, Horna J, Pariona J, Manrique J, Rubiños J, et al. Visual inspection with acetic acid for cervical cancer screening outside of low-resource settings. Rev Panam Salud Publica. 2005; 17:1-5.
9. Saleh HS. Can visual inspection with acetic acid be used as an alternative to Pap smear in screening cervical cancer? Middle East Fertil Soc J. 2014; 19(3): 187-91.
10. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136(5): E359-E86.
11. Naz U, Naseeb S, Shuja S. Concordance Between Visual Inspection with Acetic Acid Test and Pap Smear in Detection of Cervical Cancer. J Surg Pak. 2016; 21:1.
12. Ibrahim A, Aro AR, Rasch V, Pukkala E. Cervical cancer screening in primary health care setting in Sudan: a comparative study of visual inspection with acetic acid and Pap smear. Int J Womens Health. 2012; 4:67.
13. Denny L, Kuhn L, De Souza M, Pollack AE, Dupree W, Wright TC. Screen-and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial. JAMA. 2005; 294 (17): 2173-81.
14. Vadehra K, Jha R. Visual inspection using acetic acid and pap smear as a method of cervical cancer screening. J Inst Med. 2006; 28(1):36-40.
15. Begum S, Rashid M, Nessa A, Aziz M, Zakaria S, Roy J. Comparative study between Pap smear and visual inspection using acetic acid as a method of cervical cancer screening. Mymensingh Med J. 2012; 21(1):145-50.
16. Huy NVQ, Tram NVQ, Thuan DC, Vinh TQ, Thanh CN, Chuang L. The value of visual inspection with acetic acid and Pap smear in cervical cancer screening program in low resource settings–A population-based study. Gynecol Oncol Rep. 2018; 24:18-20.
17. Sinha P, Srivastava P, Srivastava A. Comparison of visual inspection with acetic acid and the pap smear for cervical cancer screening. Acta Cytologica. 2018; 62(1):34-8.
18. Mahmud G, Tasnim N, Iqbal S. Comparison of Visual Inspection with acetic acid and Pap smear in cervical cancer screening at a tertiary care hospital. J Pak Med Assoc. 2013; 63(8):1013-6.
19. Harshini V, Bhandary A, Thungha S. Comparison between Pap smear and VIA as a screening tool for cervical lesions. Indian J Pharm Biol Res. 2013; 1:55-60.

OBJECTIVE STRUCTURED CLINICAL EXAMINATION -AN EFFECTIVE TOOL OF ASSESSMENT FOR MEDICAL STUDENTS

Amir Naveed,[1] Aalia Tayyaba,[2] Zill e Huma,[3] Saima Azhar,[4] Tahira Malik,[5] Imran Jawad[6]

How to cite: Naveed A, Tayyab A, Huma Z, Azhar S, Malik T, Jawad I. Objective structured clinical examination – an effective tool for assessment for medical students. JAIMC. 2021; 19(1): 201-207.

Abstract

Background: To assess the competency of a student different tools are used. Since its introduction in 1975 by Dr. Harden and his team, OSCE (Objective structured clinical examination) has gained tremendous strides to assess the clinical competencies. Since 1975 onward OSCE has been very successfully used to assess the clinical competencies of medical student globally.

OSCE is an assessment tool in which student is observed for performance of different tasks at specified stations. In the current study perception of medical students about OSCE examination was done which shall give room for positive criticism and further improvement of the system where ever required.

Objective: To find out view of fourth and final year MBBS students of Amna Innayat Medical College Sheikhupura about OSCE.

Methodology: It was a Quantitative, cross sectional study. Questionnaire developed by Russell et al was used. Data was analyzed using SPSS.

Result : Evaluation of OSCE, two third of the students (n=100, 67.6) expressed their satisfaction about the fairness and knowledge covered during this exam. Quality of performing test question regarding the nature of the exam only 29.7% were aware. Majority 52.7% were of the view that what was taught was assessed through this exam, 50% were satisfied with the content and context for each station. based on the perception of students 54.1% of the students perceived essay type exam the easiest, however, 66.2% were in favor of essay type assessment. OSCE was considered to be fairest of all the formats 73%. Majority 68.9% considered that MCQs enhanced their learning skills.

Conclusion: To conclude this study, it is very much clear that the perception of students about OSCE as an assessment tool was very encouraging, as it not only provided them the opportunity to highlight their weaknesses but also helped them to perform well in the exam, manage time during exam and to overcome them stress which influenced their results.

Key Words: OSCE (Objective structured clinical examination) ,MCQS (Multiple choice question), Assessment Crietaria , Assessment Tool, OSPE (Objective structured practical examination)

To assess the competency of a student different tools are used.[1,2] A few decades ago long essay questions were used for assessment.[3] With the advent of new teaching strategies, new assessment tools were also developed such as, MCQs, SEQs, OSCE, OSPE etc. It was the hard work of Harden which gave the concept of MCQs, OSCE and many other tools which could be used to assess the com-petency of a student.[4]

Since its introduction in 1975 by Dr. Harden and his team, OSCE has gained tremendous strides to assess the clinical competencies.[5] Millers pyra-mids of assessment comprises of four levels knows, knows how, shows how and does.[6] The third level i.e. shows how is reflected through OSCE. Since 1975 onward OSCE has been very successfully used to assess the

1. Amir Naveed
2. Aalia Tayyba
3. Zill e Huma
4. Saima Azhar
5. Tahira Malik
6. Imran Jawad

1-4. Amna Innyat Medical College, Sheikhupura
6. University College of Medicine UOL, Lahore

Correspondence:
Dr. Amir Naveed, *Associate Professor Forensic Medicine Amna Innayat Medical College. Email:Aamirnaveed865@gmail.com*

Submission Date: 12-11-2020
1st Revision Date: 25-11-2020
Acceptance Date: 08-12-2020

clinical competencies of medical student globally.

The clinical competencies of medical students were assessed through written exams, viva voce, short and long cases in the wards through observation on the patients.

Harden emphasized that written exam can be used to assess the cognitive domain of students; focusing more on this sphere will weaken the psychomotor skills.

In viva voce i.e. oral examination criticism regarding biasness cannot be ruled out.[7,8] OSCE answers all such criticisms, and has been effectively used to assess clinical competencies of medical students.[9]

OSCE is an assessment tool in which student is observed for performance of different tasks at specified stations. In the current study perception of medical students about OSCE examination was done which shall give room for positive criticism and further improvement of the system where ever required. It shall also encourage teachers to change assessment tools where required. This assessment tool not only helps to assess the clinical skills of students but also provides opportunity to observe behavior of the student.

In the early nineties college of physician and surgeons of Pakistan introduced OCSE for assessment of the students. With the success of this instrument as an assessment tool, it was taken up by PMDC to be further incorporated into different medical colleges and universities. Currently all medical colleges in Pakistan are using this tool to assess the clinical competencies of their students. We all view this assessment tool as a useful instrument, but the perception of students has seldom been recorded. Literature search have shown few publications within the country to give an opportunity to have good view from student's point of view about this assessment tool. This provides a gap in the study in our context.

What is the perception of fourth and final year MBBS students at Amna Inayat Medical College, SHIEKHUPURA about OSCE as assess-ment tool?

METHODOLOGY

It is a quantitative, cross sectional study, conducted at Amna Inayat Medical College Sheikhupura. 148 students from fourth and final year students of MBBS were included in the study. A purposive sampling technique was used. Student appearing in the fourth and final profe-ssional MBBS examination were included. Student of any professional examination other than fourth and final year MBBS were not included in the study. Questionnaire developed by Russell et al was used. Data was analyzed using SPSS.

RESULTS

Out of 148 students who participated in the study, 66(45%) students were females and 82(55%) were male. The result has been studied under the heading as follows.

Evaluation of OSCE 10 questions

Quality of performing test question 08

Students rating of assessment format questions 12

All results are discussed below:

Students evaluated OSCE examination through a set of 10 questions, which covered an ample amount of issues related to all such exams such as fairness of exam, covering all corners of the curri-culum, time allocation for each station, stress level during exam. Table-1 provides a good view about the student's response, two third of the students (n=100, 67.6) expressed their satisfaction about the fairness and knowledge covered during this exam, graphical representation is shown in figure-1

Majority (n=74,50) were not satisfied with the time allocation for each station. Satisfaction level was very good the way the exam was administered (n=114,154). Majority agreed that although the exam was well structured (n=96,129.8) but it was stressful (n=108,73). However, majority did not agree that it is less stressful as compared to other exams (n=68,45.9). It not only compensates other formats of the exam (n=116,78.4) but also covers

wide range of clinical skills (n=96,64.9).

Majority of the students were satisfied with the quality of the exam. Regarding the nature of the exam only 29.7% were aware. Majority 52.7% were of the view that what was taught was assessed through this exam, 50% were satisfied with the content and context for each station. Results about the quality of the exam are exhibited in table-2 and figure-2.

Students rating of multiple assessment formats Students were briefed about different formats of assessment, based on the perception of students 54.1% of the students perceived essay type exam the easiest, however, 66.2% were in favor of essay type assessment. OSCE was considered to be fairest of all the formats 73%. Majority 68.9% considered that MCQs enhanced their learning skills. All these findings are exhibited in table-3 and figure-3.

Majority of the students 67.6% were satisfied about the fairness of the exam and the cognition covered, however, 64.9% were stressful about the exam.

Consensus about the quality of exam was that, 29.7% were aware about the nature of the exam, 52.7% were satisfied that the syllabus taught was asked in the exam, 58.1% were satisfied about the time allocation for each station.

Majority i.e. 60% considered OSCE an exam of practical nature which is not biased by gender or ethnicity.

More than 50% of the students were satisfied with the standard of the exam. At the same time more than 50% students considered essay exam the easiest format of assessment. However, OSCE was considered to be fairest form of assessment 73%.

68.9% perceived that learning is enhanced by

Table 1: *Students Response about OSCE*

Sr #	Question	Agree N(%)	Neutral N(%)	Disagree N(%)	No comments N(%)
1	Exam was fair	100(67.6)	40(54)	4(5.4)	4(5.4)
2	Knowledge was covered adequately	100(67.6)	36(24.3)	12(8.1)	0
3	Adequate time was provided at stations	40(27)	34(23)	74(50)	0
4	Exam was well administered	114(154)	26(35.2)	4(5.4)	4(5.4)
5	Exam was stressful	96(64.9)	24(32.4)	26(35.2)	2(1.4)
6	Exam was well structured	108(73)	26(35.2)	14(9.5)	0
7	Exam reduced failure chances	76(51.4)	42(28.4)	24(16.2)	6(4.1)
8	This exam is less stressful than other format of examination	48(32.4)	32(21.6)	68(45.9)	0
9	This exam compensate other format of exams	116(78.4)	26(17.6)	6(4.1)	0
10	Wide range of clinical skills covered	96(64.9)	32(21.6)	16(10.8)	4(2.7)

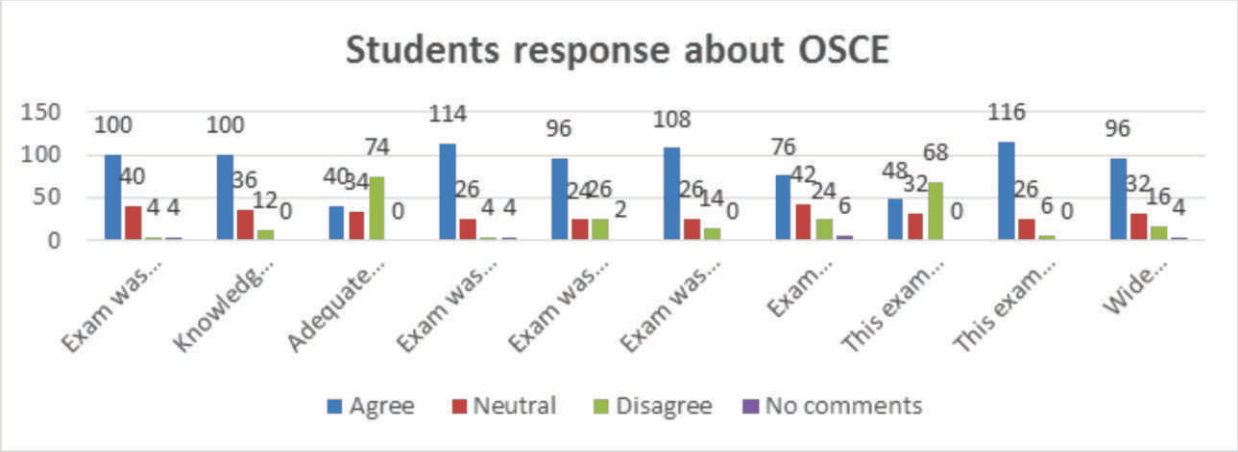


Figure-1

Table 2: Quality of Performance

Sr #	Question	Not at all N(%)	Neutral N(%)	To great extent N(%)
1	Aware about the nature of exam	34(23)	50(47.3)	62(29.7)
2	Skills assessed according to course taught	14(9.5)	56(37.8)	78(52.7)
3	Adequate time for each station	14(9.5)	48(32.4)	86(58.1)
4	Context of each station appropriate	9(4.1)	65(45.9)	74(50)
5	Instruction at each station clear	10(6.8)	48(32.4)	90(60.8)
6	Task at non-static stations were fair	12(8.1)	56(37.8)	80(54.1)
7	Sequencing was logical	10(6.8)	60(40.5)	78(52.7)
8	Exam provided appropriate learning	12(8.1)	26(17.6)	110(74.3)

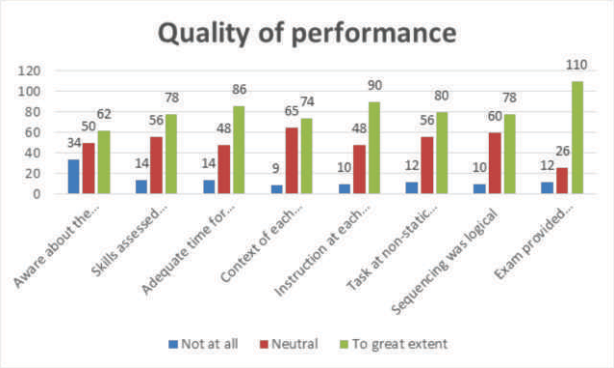


Figure-2

MCQs rather than other formats of assessment.

DISCUSSION

Since the inception of OSCE as an assessment tool by Dr Harden and his team, it has shown rapid strides and never turned back, with the passage of time and new experiments on this tool it has impro-ved and is expected to follow same pace in the future as well this was supported by Harden RM and Ahmed K in their studies.[10,11]

Table 3: Students Rating of Multiple Assessment Formats

Question-1	Which of the formats is easiest		
	Difficult N%	Undecided N%	Easy N%
MCQ	72(48.6)	46(31.1)	30(20.3)
SAQ/Essay	20(13.5)	48(32.4)	80(54.1)
OSCE	34(23)	48(45.9)	66(31.1)
VIVA	80(54.1)	40(27)	28(18.9)
Question-2	**Which of the formats is fairest**		
	Difficult N%	**Undecided N%**	**Easy N%**
MCQ	14(9.5)	36(24.3)	98(66.2)
SAQ/Essay	16(10.8)	48(32.4)	84(56.8)
OSCE	16(10.8)	24(16.2)	108(73)
VIVA	78(52.7)	48(32.4)	22(14.9)
Question-3	**Which of the formats is fairest**		
	Difficult N%	**Undecided N%**	**Easy N%**
MCQ	24(16.2)	22(14.9)	102(68.9)
SAQ/Essay	40(27)	54(36.5)	54(36.5)
OSCE	20(13.5)	36(24.3)	92(62.2)
VIVA	52(35.1)	48(32.4)	48(32.4)
Question-4	**Which of the formats enhanced learning**		
	Difficult N%	**Undecided N%**	**Easy N%**
MCQ	38(25.7)	22(14.9)	88(59.5)
SAQ/Essay	18(12.2)	32(21.6)	98(66.2)
OSCE	52(35.1)	46(31.1)	50(33.8)
VIVA	78(52.7)	32(21.6)	38(25.7)

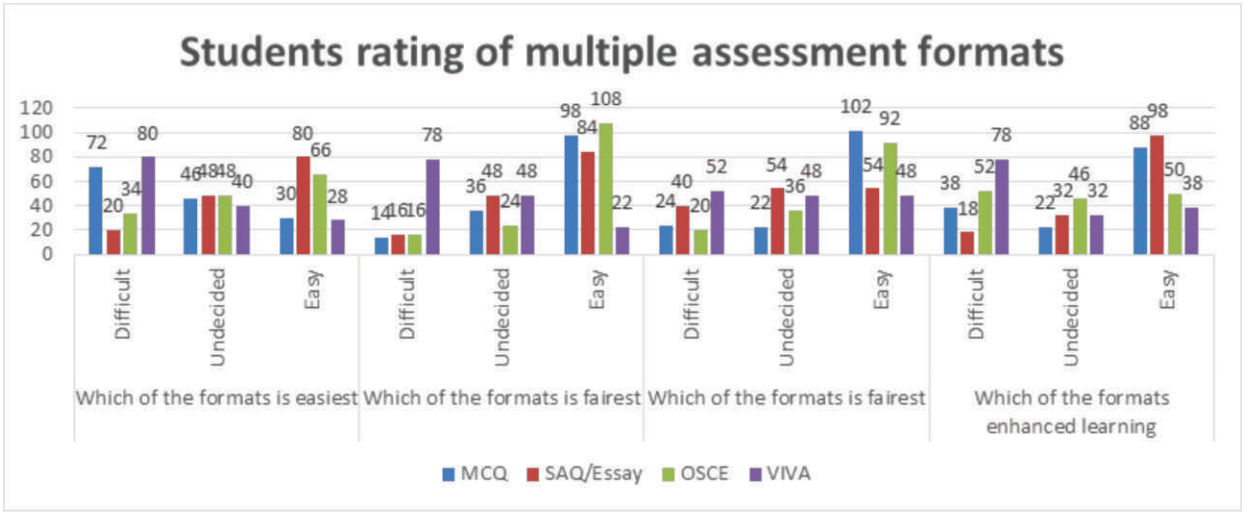


Figure-3

This study at Amna Innayut Medical college Sheikhupura involving fourth and final year MBBS students about their views for clinical assessment using OSCE as a tool was recorded. This helped a lot in the local context as majority of the studies have been conducted in the western world and literature on OSCE as an assessment tool is quite scarce in the subcontinent.

Chong L, Taylor S et al. in their study agreed that OSCE as an assessment tool was viewed from different dimensions by the students. Majority of the students were satisfied that the element of biasness was eliminated, and with good management the quality and fairness of the exam is improved, it also covers reasonably good area of cognition.[12]

McWilliam P.L. in his study has stressed about the satisfaction of students that the clinical skills which they have practiced throughout the session were assessed in a well-structured way through OSCE.[13]

Hutton M, El-Nemer A and Epstein RM are of the view about the time management studnets are given for perform given task at each OSCE station. More than 50% of the students were under extreme stress during the assessment; this directed them toward easy assessment ways such as long essay questions. An added advantage pointed out by the students was that this format of assessment compensated other formats of assessment during the same examination.[14-16]

This assessment format proved to be an effect way for clinical skill assessment, however, it did not add to their knowledge as compared to MCQs, which improved their cognition level this negative effect was also pointed by Moeen-uz-Zafar Khan BM in his study.[17] The chances of success in this format of assessment is fairly well as compared to other formats of assessment it was also supported by Wallenstein J in his study.[18] This increase in the success rate was due to multiple factors. Students expressed that the format was clearly explained to them before the start of exam, environment was conducive, time allocation for stations was adequate, exam was sequenced and managed in such a way which improved the quality of the exam, it was supported by Iramaneerat C in his study.[19]

The Accreditation council for graduate medical education (ACGME) has regarded OSCE as second best tool for assessment of clinical skills.[20]

Beckert L in his study supports that OSCE has improved the overall result of the students as it has proved to be an effective assessment tool and it has compensated the other formats of the same exam.[21]

Turner JL has also supported the quality and fairness of the OSCE is above rest of the formats of the exam which has exhibited the reliability and validity of the exam.[12,22]

Majority of the students were satisfied with the assessment of OCSE because according to their perception assessment with the traditional system was poor and judgment of the competencies of the student was not on equal bases.

Bokken L, Rethans J-J, Scherpbier AJ, van der Vleuten CP in their study emphasized same points which were elaborated in our study, that OSCE covered a wide range of cognition and psychomotor skills than the other formats of exams, to an extent it also highlighted their weakness and strengths which enabled them to improve for future assessment.[23]

OSCE provided them the opportunity to manage the exam, this was due to pre-exam awareness about the exam as they were well aware about the nature of the exam, the time allowed for each station this was supported by a study conducted by Haider I, Khan A, Imam SM, Ajmal F, Khan M, Ayub M.[24] However, all such factors did not relieve the stress of the students during exam.

Overall the students were very much satisfied by this examination system and wished that such formats of examination should be promoted and students and staff should be encouraged and facilitated to continue with such systems of assessment.

CONCLUSION

To conclude this study, it is very much clear that the perception of students about OSCE as an assess-

ment tool was very encouraging, as it not only provided them the opportunity to highlight their weaknesses but also helped them to perform well in the exam, manage time during exam and to overcome them stress which influenced their results.

Acknowledgments

Authors are thankful to GYNAE and Forensic department Amna Inayat Medical College for facilitation and support in the study. A special thanks to Prof Asma Gul for her guidance.

Conflict of Interest Statement

No potential conflict of interest relevant to this article was reported.

Funding Source

No source of funding relevant to this article was reported.

REFERENCE

1. Duffy K. Failing students: a qualitative study of factors that influence the decisions regarding assessment of students' competence in practice: Citeseer; 2003.
2. Ilic D. Assessing competency in evidence based practice: strengths and limitations of current tools in practice. BMC medical education. 2009;9(1):53.
3. Pepple DJ, Young LE, Carroll RG. A comparison of student performance in multiple-choice and long essay questions in the MBBS stage I physiology examination at the University of the West Indies (Mona Campus). Advances in physiology education. 2010;34(2):86-9.
4. Shumway JM, Harden RM. AMEE Guide No. 25: The assessment of learning outcomes for the competent and reflective physician. Medical teacher. 2003; 25(6):569-84.
5. Munoz LQ, O'Byrne C, Pugsley J, Austin Z. Reliability, validity, and generalizability of an objective structured clinical examination (OSCE) for assessment of entry-to-practice in pharmacy. Pharmacy Education. 2004;5.
6. Cruess RL, Cruess SR, Steinert Y. Amending Miller's pyramid to include professional identity formation. Academic Medicine. 2016;91(2):180-5.
7. Davis MH, Karunathilake I. The place of the oral examination in today's assessment systems. Medical Teacher. 2005;27(4):294-7.
8. Rehman R, Syed S, Iqbal A, Rehan RR. Perception and performance of medical students in Objective structured practical examination and viva voce. Pakistan Journal of Physiology. 2012;8(2):33-6.
9. Khattab AD, Rawlings B. Assessing nurse practitioner students using a modified objective structured clinical examination (OSCE). Nurse Education Today. 2001;21(7):541-50.
10. Harden RM, Gleeson F. Assessment of clinical competence using an objective structured clinical examination (OSCE). Medical education. 1979; 13(1): 39-54.
11. Ahmed K, Miskovic D, Darzi A, Athanasiou T, Hanna GB. Observational tools for assessment of procedural skills: a systematic review. The American Journal of Surgery. 2011;202(4):469-80. e6.
12. Chong L, Taylor S et al. The sight and insights of examiners in objective structured clinical examinations .J Educ Eval Health Prof.2017:14:34. doi: 10.3352/jeehp.2017.14.34
13. McWILLIAM PL, Botwinski CA. identifying Strengths and weaknesses in the utilization of objective Structured Clinical Examination (osce) in a nursing Program. Nursing education perspectives. 2012;33(1):35-9.
14. Hutton M, Coben D, Hall C, Rowe D, Sabin M, Weeks K, et al. Numeracy for nursing, report of a pilot study to compare outcomes of two practical simulation tools–An online medication dosage assessment and practical assessment in the style of objective structured clinical examination. Nurse Education Today. 2010;30(7):608-14.
15. Majumder MAA, Kumar A, Krishnamurthy K, Ojeh N, Adams OP,Sa B. An evaluative study of objective structured clinical examination(OSCE):students and examiners perspectives.Advances in Medical Education and practice.2019: 10.P 387-397. doi.org/ 10.2147/AMEP.S197275
16. Epstein RM. Assessment in medical education. N Engl J Med. 2007;2007(356):387-96.
17. Moeen-uz-Zafar Khan BM. Evaluation of modified essay questions (MEQ) and multiple choice questions (MCQ) as a tool for assessing the cognitive skills of undergraduate medical students. International journal of health sciences. 2011;5(1):39.
18. Wallenstein J, Heron S, Santen S, Shayne P, Ander D. A core competency–based objective structured clinical examination (OSCE) can predict future resident performance. Academic Emergency Medicine. 2010;17:S67-S71.
19. Elfaki OA, Alhummayed S.Medical students per-

ception of OSCE at the Department of internal Medicine, College of Medicine, King Khalid University, Abha , KSA. J Coll physicians Surg Pak. 2016; 26(2):158-159.doi:02.2016/JCPSP.158159

20. Swick S, Hall S, Beresin E. Assessing the ACGME competencies in psychiatry training programs. Academic Psychiatry. 2006;30(4):330-51.
21. Beckert L, Wilkinson TJ, Sainsbury R. A needs-based study and examination skills course improves students' performance. Medical Education. 2003; 37(5):424-8.
22. Turner JL, Dankoski ME. Objective structured clinical exams: a critical review. Fam Med. 2008; 40(8): 574-8.
23. Bokken L, Rethans J-J, Scherpbier AJ, van der Vleuten CP. Strengths and weaknesses of simulated and real patients in the teaching of skills to medical students: a review. Simulation in Healthcare. 2008; 3(3):161-9.
24. Haider I, Khan A, Imam SM, Ajmal F, Khan M, Ayub M. Perceptions of Final Professional MBBS Students and their Examiners about Objective Structured Clinical Examination (OSCE): A Combined Examiner and Examinee Survey. Journal of Medical Sciences. 2016; 24(4): 206-11.
25. Skrzypek A, Szeliga M, Stalmach-Przygoda A, et al. The Objective structured Clinical examination (OSCE) from perspective of 3rd year's medical students- a pilot study. Folia Med Cracov.2017; 57(3):67-75.

PREMICROSCOPIC ERRORS IN BREAST TUMOR SPECIMENS; AN EXPERIENCE FROM HISTOPATHOLOGY DEPARTMENT OF KING EDWARD MEDICAL UNIVERSITY, LAHORE

Fakeha Rehman,[1] Samreen Hameed,[2] Muhammad Imran[3]

How to cite: Rehman F, Hameed S, Imran M. Premicroscopic errors in breast tumor specimens: an experience from histopathology department of King Edward Medical University, Lahore. JAIMC. 2021; 19(1): 208-211.

Abstract

Background: Handling of specimens from breast in gross room is of utmost importance as any negligence in collection, requisition, fixation, inking or specimen cutup till preparation of slides may significantly affect the decision in management of the patient.

Objective: To document near miss events and errors in handling of surgical specimens from patients with breast lesions and the factors resulting in generation of these events.

Methodology: A cross-sectional study was conducted in histopathology section of pathology department of King Edward Medical University, Lahore. A total of 56 tumor specimens including different types of biopsies and resection specimens were included in the study. Pre-analytical errors like; crushed, fragmented biopsies, inappropriate fixative and labeling errors some of the analytical errors include inappropriate recording of specimen dimensions, insufficient tumor sampling, inadequate decalcification and margin selection.

Results: Most of the errors observed during pre-analytical phase significantly affected the interpretation of gross examination findings. Errors during analytical phase mainly resulted from negligence, inappropriate training, and lack of supervision of the designated staff handling the gross specimens.

Conclusion: Standard operating procedures for grossing the tumor specimens must be followed in true spirit. Individuals involved in the specimen grossing have to be fully trained and vigilant in performing their assigned task so as to avoid potential harm to the cancer patient as a result of any mischievous act and negligence during grossing of tumor specimen.

Key Words: Errors, breast, gross room, histopathology, pre-microscopic

All the surgical specimens received at the reception are subjected to gross examination and sectioning in the gross room. An accurate histopathological diagnosis is highly dependent on precise gross examination and appropriate section selection from the lesion. With new advents in the field of histopathology, more emphasis on patient safety is being given especially to minimize errors during the process of slide preparation.[1]

Pre-analytical and analytical errors may result in serious harms related to both treatment and prognosis of the patients with breast cancer. Documentation of these errors and their timely identification results in provision of authentic results and an improved quality of laboratory.[2,3] A better understanding of the spectrum of the surgical specimen management errors is needed to inform the design of system that are effective in preventing the occurrence of these errors.

Irrespective of advances in molecular and various ancillary techniques, histopathological diagnosis is still taken as gold standard in provision of critical information required for treatment and

1. Fakeha Rehman 2. Samreen Hameed
3. Muhammad Imran
1&2: Department of Pathology, King Edward Medical University, Lahore, Pakistan.
3. Department of Pathology, Allama Iqbal Medical College, Lahore, Pakistan.

Correspondence:
Dr. Fakeha Rehman, *Assistant Professor, Pathology Department, King Edward Medical University, Email: sohnia@gmail.com*

Submission Date: 18-11-2020
1st Revision Date: 14-12-2020
2nd Revision Date: 20-12-2020
Acceptance Date: 26-12-2020

prognosis of the patients. Postgraduate residents in histopathology are fortunate to have easy access to the guidelines and protocols for specimen submission and handling in the histopathology laboratories, as recommended by the College of American Pathologists (CAP).[4,5,6]

The foremost step in handling of breast specimens is the accurate labeling of the specimen(s) with provision of relevant clinical information. Transport time, cold ischemia time, warm ischemia time and fixation and processing time not only affects the quality of the tissue section but the results of hormonal receptors status as well.[5,6]

Developing countries face a lot of challenges in ensuring good quality laboratory services in the form of inappropriate human resources, financial constraints to buy good quality reagents, equipments and participation in external quality assurance programs.[6]

Local data lacks in this regard therefore this study is hereby designed to document the near miss events and errors related to the pre-microscopic handling of breast specimens and the factors resulting in these events in our setup.

METHODOLOGY

A cross-sectional study was conducted in histopathology section of Pathology department. A total of 56 tumor specimens including different types of biopsies, lumpectomies and resection specimens were assessed during requisition, and grossing in the histopathology laboratory. Data was collected using a pre-designed questionnaire prepared with the help of subject specialists and extensive literature search for its content validity. We observed the specimens during six working days of the laboratory routine with special focus on handling of breast specimens

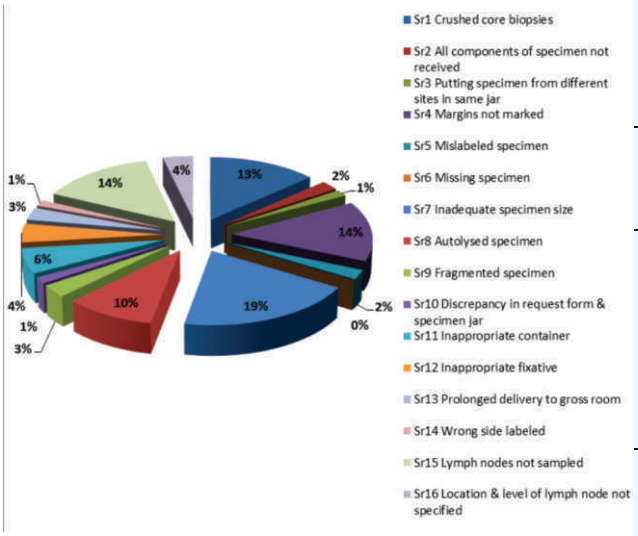


Figure1: *Pre-Analytical Errors in Breast Specimens*

Table 1: *Classification Of Analytical Errors*

Stage in process	Error Code	Near-Miss Events & Errors	No. of errors
Specimen orientation (So)	So1	Unlabeled specimen	4
	So2	Distorted specimen	5
	So3	Not recording number of cores	08
	So4	Not recording weight of the specimen	56
Ink application (I)	I1	Too heavy ink	26
	I2	Poor quality of ink	5
	I3	Inadequate specimen drying during ink application	17
	I4	Inappropriate ink fixation	29
Margin selection (Mrg)	Mrg1	Wrong margin selection	11
	Mrg2	Margins not taken	7
	Mrg3	Putting different margins in same cassette	0
Sample size	SS1	Inappropriate specimen dimensions	13
	SS2	Inappropriate tumor dimensions	17
	SS3	Inappropriate recording of tumor distance from margin	19
Section size (Sc)	Sc1	Too thick section	22
	Sc2	Inappropriate section size	23
Cassette selection (Cst)	Cst1	Inappropriate cassette selection	11
	Cst2	Inappropriate cassette lid closure	19
	Cst3	Over stuffing cassette with tissue	36
	Cs4	Mislabeling cassettes	06
Specimen fixation (Sf)	Sf1	Sectioning unfixed specimen	08
	Sf2	Prolonged fixation	02
	Sf3	Inappropriate fixative selection	00
Tissue Sampling (Ts)	Ts1	Missing lesion on gross	02
	Ts2	Inadequate section from tumor (not following CAP cancer protocol)	09
	Ts3	Inappropriate sections from adjacent parenchyma	13
	Ts4	Missing satellite nodules	01
Removal of staple/suture from specimen (Rs)	Rs1	Inadequate removal of staples or sutures from specimen	00
	Rs2	Tissue distortion during staple/suture removal	00

by reception and technical staff and resident pathologists. All the data was entered using SPSS version 21.

RESULTS

Majority of the pre-analytical errors in specimen submission were either due to delayed transport to the histopathology reception, use of inappropriate fixative and container and missing or incomplete information on request form or specimen jar. (Figure 1) Whereas, analytical errors in majority were as a result of lack of supervision, negligence of the handling staff and technical errors related to the quality of reagents and instrumentation. (Table 1) Tissue specimens may range from tiny biopsies to large complete resections. The number of fragments must be documented, the type of biopsy, e.g., shave, needle or core biopsies, and whether the specimens represent tissue or even foreign material. In processing the contents of a container, one should record the number of fragments and try not to use terms such as multiple or numerous. Errors in lymph node dissection were mainly because of inadequate sampling and fixation. (Figure 2)

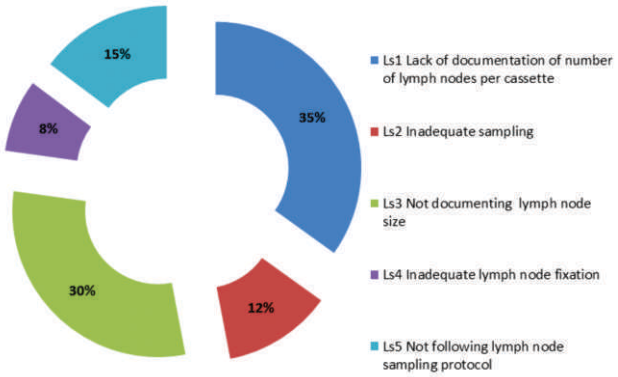


Figure 2: *Errors in Lymph Node Sampling*

DISCUSSION

Factors contributing to delays in transporting specimens included heavy workload on clinical side and lack of communication between clinical and laboratory staff. Majority of the errors during specimen transport and submission of specimens were encountered in late hours during evening and night shifts. Errors in specimen analysis were caused by numerous factors, including inappropriate order entry, inadequate specimen quantity or quality, miscommunication between the reception staff and laboratory staff and shift changes. In cases in which the specimens were lost in the laboratory, there was often more than one specimen and/or different sizes of specimens in the same container. [4,5,6,7]

Various studies have revealed that variation in cold ischemia time, duration of fixation, and other factors that can alter DNA, RNA, and proteins in the specimen that can result in erroneous interpretation of the results. [4,12,13]

American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP) has provided guidelines and recommendations for tumor marker testing in patients with breast cancer. Surgeons and operation theatre assistants have the responsibility to completely fill the request proforma, should effectively monitor the volume of fixative, selection of appropriate container for the specimen and the time to fixation from surgery (cold ischemia time) and transport to pathology reception as these all factors significantly affect the quality of biomarker reporting of the breast cancer cases.

The importance of technical staff especially grossing assistant cannot be overstated as maintaining the chain of case identity, following cassette allocation key and effective coordination with grossing resident helps in preventing identification errors. Resident should also follow guidelines and cancer protocols for gross dissection of breast specimens. There should be strict compliance of the staff working in reception and grossing area with all the standard operating protocols and work instructions.[11,12]

Lastly, quality control is mandatory if we intend to improve the quality of the reports and customer satisfaction with our services. This can be achieved only by following SOPs and regular training of the staff involved in receiving and handling of the specimens. Lean six sigma methodologies can be adopted to streamline the process flow and to reduce

time waste and errors. Effective monitoring of the staff performance, recording of error log books and provision of a blame free environment helps in improving efficiency of the both the technical staff and pathologists. Senior pathologists should supervise the junior residents and encourage them to participate in journal clubs, multidisciplinary meetings, case presentations and clinicopathological conferences so that the importance of an authentic report in deciding patient prognosis and treatment can be stressed upon. Documentation of external schemes of accreditation such as CPA is appropriate for the laboratory as a whole. [13,14,15]

CONCLUSION

This study provides an insight to the important issues related to the handling of breast specimens in histopathology laboratory. Each laboratory should develop written standards and standard operating procedures for collection and subsequent handling based on the types of specimens received. The technical staff and residents should be vigilant and competent enough to process different types of specimen as per protocol.

REFERENCES

1. Shet T, Patil A, Desai S. Breast. In: Desai S, Bal M, Rekhi B, Jambhekar NA, editors. Grossing of Surgical Oncology Specimens: A Practical Guide Towards Complete Pathology Training. 1st ed. Tata Memorial Hospital; 2012. p. 56-69
2. Compton CC. Quality and patient safety in the diagnosis of breast cancer. Clin Biochem 2013;46 (13):1180–1186.
3. Yildiz-Aktas IZ, Dabbs DJ, Bhargava R. The effect of cold ischemic time on the immunohistochemical evaluation of estrogen receptor, progesterone receptor, and HER2 expression in invasive breast carcinoma. Mod Pathol 2012; 25: 1098-105.
4. Eltoum I, Fredenburgh J, Grizzle WE. Advanced concepts in fixation: effects of fixation on immunohistochemistry, reversibility of fixation and recovery of proteins, nucleic acids, and other molecules from fixed and processed tissues, developmental methods of fixation. J Histotechnology 2001a; 24(3): 201–210.
5. Taffurelli M, Montroni I, Santini D. Effectiveness of sentinel lymph node intraoperative examination in 753 women with breast cancer: Are we overtreating patients? Ann Surg 2012; 255: 976-80.
6. Enriquez RE, Kelly LJ. The varied and useful role of the pathologists' assistant. MLO: medical laboratory observer 1991; 23(3):33–34. 36,38. [PubMed: 10110206]
7. Shet T, Pai T, Wadasadawala T, Nair N and Gulia S. Grossing and reporting of breast cancer specimens: an evidence based approach. Ind J Cancer 2020; 57(2): 144-157.
8. Troxel DB. Medicolegal aspects of error in pathology. Archives of pathology & laboratory medicine 2006; 130(5):617–619. [PubMed: 16683874]
9. Westra WH, Hruban RH, Phelps TH, Isacson C, Askin FB. Surgical Pathology Dissection: An Illustrated Guide. Springer. 2003 Argani P. Breast. Annals of diagnostic pathology 2nd ed. Springer; 2003. p. 132-40. [PubMed: 12089731].
10. Fitzgibbons PL, Bose S, Yunn-Yi Chen, Connolly JL, de Baca ME, Edgerton M, et al. Protocol for the examination of specimens from patients with invasive carcinoma of the breast Jan 2020. As published on www.cap.org/cancerprotocol. [Last accessed on 2020 May 1]
11. Troxel DB. Error in surgical pathology. The American journal of surgical pathology 2004; 28(8):1092–1095. [PubMed: 15252317]
12. Selvarajan S, Bay BH, Choo A, Chuah KL, Sivaswaren CR, Tien SL, Wong CY, Tan PH. Effect of fixation period on HER2/neu gene amplification detected by fluorescence in situ hybridization in invasive breast carcinoma. J Histochem Cytochem 2002; 50(12):1693–1696. [PubMed: 12486093]
13. Spruessel A, Steimann G, Jung M, Lee SA, Carr T, Fentz AK, Spangenberg J, Zornig C, Juhl HH, David KA. Tissue ischemia time affects gene and protein expression patterns within minutes following surgical tumor excision. BioTechniques 2004; 36(6): 1030– 1037. [PubMed: 15211754]
14. Samulski TD, Mantone K, Livolsi V, Patel K and Baloch Z. Patient safety curriculum for anatomical pathology trainees: recommendations based on institutional experiences. Adv Anat Pathol 2016; 23: 112-117.
15. Westguard S. Prioritizing risk analysis quality control plans based on sigma metrics. Clin Lab Med 2013; 33: 41-53.

FREQUENCY OF MAIN CONTRIBUTING FACTORS FOR UNDER VACCINATION IN CHILDREN VISITING JINNAH HOSPITAL LAHORE

Asif Ali Abrar,[1] Sonia Zofishan,[2] Ayesha Arif[3]

How to cite: Abrar AA, Zofishan S, Arif A. Frequency of main contributing factors for under vaccination in children visiting Jinnah Hospital Lahore. JAIMC. 2021; 19(1): 212-215.

Abstract

Background : A person becomes immune or resistant against an infectious disease when a vaccine is administered this process is known as immunization. Immune system of body is stimulated by the administration of vaccines.This protects the person against subsequent infection or disease.

Objectives: to find the frequency of main contributing factors for under vaccination in children visiting Jinnah Hospital Lahore.

Methodology: Cross-sectional type of study was conducted in Jinnah Hospital Lahore from

21-11-2017 to 20-04-2018.Written informed consent was obtained from the parents of 120 patients fulfilling inclusion and exclusion criteria from the Pediatric department Jinnah Hospital Lahore after explaining the details of study and its associated benefits and risks .Information regarding their demographic data was noted in the proforma. Patient, who were under vaccinated or non-vaccinated, were selected and main contributing factors for under vaccination were evaluated by their parents.

Results: Mean age of child was 22.491 SD 12.43 with the minimum age of 4 months and the maximum age of 57 months. 91.0% children were less than 30 moths. 46.7% were male and 53.2% were female. 36.7% mothers were illiterate 37.5% were literate and 25.8% were matric and above.

Conclusion The main factor for non vaccination in our community was child sickness (59.2%) followed by religious taboo (50.2%), lake of knowledge (44.2%), fear of side effects (43.3%).

Key Words: EPI, vaccination, vaccination refusal, vaccines

Immunization is one of the integral elemental part of health prevention and a very frugal, economical, practical way of improving the quality of health by reducing the mortality and combating the poverty thereby entailing towards the socioeconomic prog-ress of any country. Vaccination programs directly benefit the immunized child. They also indirectly benefit unimmunized persons through community (herd) immunity.[1,2] The Expanded Program on Immunization was launched by World Health Organization in 1974. Its aim was to save children from life threatening and debilitating childhood diseases[3]. The Expanded Program on Immunization was started in Pakistan in 1978. The main goal was to eradicate polio by 2012, wipe out measles and neonatal tetanus by 2015. The goal also aimed at reducing the inci-dence of other diseases which can be prevented by administration of vaccines.[4] The vaccine preventable diseases are responsible for 27% deaths in less than 5 years age group.[5] The noteworthiness of EPI can connoted by the fact that if the EPI program is suspended it will result in death of approximately around 1000 children under the age of 5 years.[5] A lot of child specialists are

1. Asif Ali Abrar 2. Sonia Zofishan
3. Ayesha Arif
1. Tehsil Headquarter THQ Hospital Ahmad Pur Sial Jhang
2,3. *Department of Paediatrics , Jinnah Hospital, Allama Iqbal Medical College, Lahore*

Correspondence:
Dr. Asif Ali Abrar, *Tehsil Headquarter THQ Hospital Ahmad Pur Sial Jhang*

Submission Date: 29-11-2020
1st Revision Date: 12-12-2020
Acceptance Date: 19-12-2020

witnessing an outrage and dramatic increase in cases of vaccine hesitancy and refusal. A sort of "cultural epidemic" is on its way out and has been escalating over the recent years. This resultantly gradually affects the families of children. Furthermore, in recent trend the number of parents who apprehend that vaccination is not safe and necessary is skyrocketing. Though vaccination has been extensively proven and acknowledged to be one of the biggest, safest, and most successful public health measures ever adopted. Child specialists have unprecedented unparelled impact on parental vaccine decisions. However, the vaccine hesitancy phenomenon is cumbersome and perplex its difficult to change the apprehension of people and their decisions.[6,7] Jinnah Hospital Lahore is a tertiary care centre where patients from all parts of the country are being treated. In Pakistan the data relating to the success and failure rate of EPI in eradicating preventable childhood illnesses is limited not many studies are available at the time being. I want to study the factor for under vaccination including fear of side effects, lack of knowledge, inaccessible health facility, non availability of vaccine, religious taboos and child sickness, which will help in identifying the various reasons and taking appropriate measures to prevent morbidity and mortality in children.

Children who had either not been vaccinated (non-vaccinated) or had failed to complete the course of vaccination (partially vaccinated) according to their ages per EPI schedule were taken as "under vaccinanated".

Major contributing factors for under vaccination:

A : fear of side effects.
B: Lack of knowledge
C: Inaccessible health facility.
D: non availability of vaccines
E : Religious taboos
F : Child sickness

METHODOLOGY

At the Department of Paediatrics Jinnah hospital Lahore a descriptive cross sectional study was done from 21-11-2017 to 20-04-2018 six months after approval of synopsis 120 cases those fulfilling the inclusion criteria were selected through non probability consecutive sampling calculated using 95% confidence level, 7% margin of error and expected percentage of lack of knowledge as 18.1%.[8]

Parents of under vaccinated children whose accompanying child was at least two months of age, but not more than 5 years of either gender presenting for routine check-up were approached and included during the period of study. Patients who were not accompanied by either parents, suffered either fits or hypersensitivity reactions during the last vaccination were excluded from the study. Study was started after taking permission from the institutional ethical committee. 120 patients who fulfill inclusion and exclusion criteria were recruited for the study. The details of study and its associated benefits and risks were explained and then written informed consents were taken from the parents / guardian. Interview was taken from the parents in the outpatient department and indoor department. The status of vaccination of the accompanying child was verified and determined from the vaccination card and proper documents. Cases in which the document was missing or not available, the parents were inquired about the status of vaccination.

The study proforma was comprised of two sections. Section A and Section B.Section A contained the bio-data of the current child age, gender. Whilst, in section B the parents were interrogated and requested for regarding the reasons that prevented them from getting their child vaccinated. The parents were inquired regarding their views, myths and perceptions regarding vaccination at the end of each interview and all their concerns were addressed. The need for vaccination was stressed in every session. Positiviely. Henceforth, our study did not provide an exploratory analysis, but also served as a didactic tool.

Data from the questionnaire was entered in SPSS version 17.0 for analysis. Numerical variable

which includes age was shown as mean and standard deviation. Qualitative descriptive variables which here imply gender, fear of side effects, lack of knowledge, inaccessible health facility, non-availability of vaccine, religious taboos and child sickness on the day of vaccination were shown as frequencies and percentages. Stratification of the data was done for gender of child, socioeconomic status and education of mother to sort out the issue of effect modifiers. $p < 0.05$ was taken as statistically significant and after the stratification of variables Chi-square test was applied.

RESULTS

Mean age of child was 22.491 SD 12.43 with the minimum age of 4 months and the maximum age of 57 months. 91.0% children were less than 30 moths. 46.7% were male and 53.2% were female. 36.7% mothers were illiterate 37.5% were literate and 25.8% were matric and above.

Table 1: *Reasons for Non-Vaccination and Gender Crosstabulation*

Reasons for non-Vaccination	Gender		Total	P value
	Male	Female		
Fear of side effects	27	25	52	p = .313
	48.2%	39.1%		
Lack of Knowledge	23	30	53	p =.523
	41.1%	46.9%		
Inaccessible Health Facility	14	26	40	p =.070
	25.0%	40.6%		
Non availability of vaccine	18	31	49	p =.070
	32.1%	48.4%		
Religious taboos	25	36	61	p =.204
	44.6%	56.3%		
Child sickness	40	31	71	p =.011
	71.4%	48.4%		
Total	56	64	120	

Table 2: *Reasons for Non-Vaccination and Education of Mother Cross Tabulation*

Reasons for non-Vaccination	Mother education			Total	Chi-square P value
	Illiterate	Middle	Matric and above		
Fear of side effects	21	17	14	52	p =.621
	47.7%	37.8%	45.2%		
Lack of Knowledge	25	19	9	53	p =.050
	56.8%	42.2%	29.0%		
Inaccessible Health Facility	15	14	11	40	p =.916
	34.1%	31.1%	35.5%		
Non availability of vaccine	15	19	15	49	p =.450
	34.1%	42.2%	48.4%		
Religious taboos	28	20	13	61	p =.100
	63.6%	44.4%	41.9%		
Child sickness	23	26	22	71	p =.261
	52.3%	57.8%	71.0%		
Total	44	45	31	120	

Table 3: *Reasons for Non-Vaccination and Socio-Economic Cross Tabulation*

Reasons for non-Vaccination	Socio-economic status			Total	Chi-square P value
	Low (Rs: 15000/ month)	Middle (Rs: 15000 - 50000 / month)	High (> Rs:50000 / month)		
Fear of side effects	17	27	8	52	p =.252
	37.0%	51.9%	36.4%		
Lack of Knowledge	21	25	7	53	p =.422
	45.7%	48.1%	31.8%		
Inaccessible Health Facility	13	17	10	40	p =.368
	28.3%	32.7%	45.5%		
Non availability of vaccine	19	20	10	49	p =.852
	41.3%	38.5%	45.5%		
Religious taboos	26	26	9	61	p =.478
	56.5%	50.0%	40.9%		
Child sickness	29	30	12	71	p =.768
	63.0%	57.7%	54.5%		
Total	46	52	22	120	

DISCUSSION

A lot of different studies have been done to uncover the crucial and main reasons for vaccination refusal or hesitancy in many parts of the world. There is a study done by Imran et al, which showed that the number of parents who did not vaccinate their children because of the fear of side effects was 33% but in our study, it was 43.3%. Health facility was inaccessible for 19% individuals as compared to our study which showed 33.3% and 23% experienced non availability of vaccine but in our data, this was 40.8%[9]. In another study by Sheikh et al on vaccination. This study showed that chief ,elemental

and foremost reasons for non vaccination were lack of knowledge (18.1%) whereas the second prime reason for non vaccination was religious taboos (31.4 %)but in our study, the most common reason for non vaccination was child sickness on particular day of vaccination and missed vaccination (59.2%) and second reason of prime importance for non vaccination was religious taboos (50.2%).[8] A study by Dindod et al , showed that the foremost common reason for partial immunization were sick child as (68.9%) followed by vaccine not available as (32.3%) and proceeded by being outside on the day of session as (31.11%) but in our study, non vaccination due to child sickness was 59.2% followed by religious taboos 50.2% and lack of knowledge as (44.2%).[10] There is a study from Philippines on vaccination according to which maternal illiteracy is the vital reason for under vaccination.[11]

In every part of the world, there are different reasons for non vaccination of the children. In my opinion, whatever the reason for non vaccination was, our main concern is to minimize the vaccine refusal and to convince the parents for vaccination. We have to do this with the help of awareness programs in each community, with the help of social media e.g. newspaper, television, publication and to take action against those who are doing negative propaganda against immunization and we have to banned all negative material published without evidence against vaccination.

CONCLUSION

The main factor for non vaccination in our community was child sickness (59.2%) followed by religious taboo (50.2%), lack of knowledge (44.2%), fear of side effects (43.3%). Among the children, slightly more female(53.33) were non-vaccinated as compared to male. Most of the families belong to middle class socio economic status (43.33%) with the mother qualification of middle passed(37.5%). At each encounter, providers should listen to parental concerns to identify sources of misinformation or other factors that may lead to vaccine hesitancy. Providers can then provide individualized education to address specific concerns or misconceptions. Education should be multifaceted, with providers answering questions unambiguously, avoiding complicated statistics, and providing information that is easily understood and "personal." Some parents may find the information in the Vaccine Information Statements adequate to address their needs, but others may require more detailed scientific information or may find simple question-and-answer pamphlets or personal testimonials from vaccine advocates more helpful.[12,13]

REFERENCES

1. Meissner HC. Why is herd immunity so important. AAP News 2015; 36:14.
2. Rashid H, Khandaker G, Booy R. Vaccination and herd immunity: what more do we know? CurrOpin Infect Dis 2012; 25:243.
3. World Health Organization: Immunization service delivery. Available at: http://www.who.int/ immunization delivery/en/. Last accessed 17th July, 2017.
4. End polio: EPI. Available at: http:// www.endpolio.com.pk/polio-in-pakistan/epiupdates/.Last accessed 17th July, 2017.
5. Health department.EPI, Available at: http:// health.punjab.gov.pk/?q=epi. Last accessed 17th July, 2017.
6. KestenbaumLA,Feemster KA. Identifying and addressing vaccine hesitancy. Pediatr Ann 2015; 44: e71-5.
7. Salmon DA,DudleyMZ,GlanzJM,Omer SB. Vaccine hesitancy: causes, consequences, and a call to action. Am J Prev Med 2015;49 (6 suppl 4):S391-8.
8. Sheikh A,Iqbal B,Ehtamam A,Rahim M,Sheikh HA,Usmani HA,et al. Reason for non-vaccination in pediatric patients visiting tertiary care centers in polio-prone country. Arch Public Health, 2013 Jul13;71(1):19.
9. Imran SS., Ramzan M,Maqsood I. Status of immunization of children and factors related to partial and non-immunization.Biomedia,2014 Sep 30;3:1-4.
10. Dindod SM,Makwana NR,Yadaw SB. Knowledge of caretakers about routine immunization and reason for partial immunization in rural areas of Jamnagar District. IndJMed Public Health 2014;4:57-61.
11. BondyJN, ThindA, KovalJJ, Speechley KN. Identifying the determinants of childhood immunization in the Philippines 2009,27(1):169-175.
12. Healy CM, Pickering LK. How to communicate with vaccine-hesitant parents. Pediatrics 2011; 127 Suppl 1:S127.
13. Chen RT, Vaccine risks: real, perceived and unknown. Vaccine 1999; 17 Suppl 3:S41.
14. Sheikh A,Iqbal B,Ehtamam A,Rahim M,Sheikh HA,Usmani HA,et al. Reason for non-vaccination in pediatric patients visiting tertiary care centers in polio-prone country. Arch Public Health,2013 Jul 13; 71(1):19.

COMPLICATIONS AND REASONS FOR DISCONTINUAUTION OF PPIUCD IN A TERTIARY HEALTH FACILITY

Zahida Noreen,[1] Robina Tariq,[2] Aymen Javed,[3] Alia Bashir[4]

How to cite: Noreen Z, Tariq R, Javed A, Bashir A. Complications and reasons for discontinuation of PPIUCD in a tertiary health facility. JAIMC. 2021; 19(1): 216-220.

Abstract

Background: Postpartum intrauterine contraceptive devices (PPIUCD) has emerged as a important component of postpartum family planning programs. Our aim was to study the satisfaction level of the women who accepted PPIUCD and to study the complications/problems which made them request for the removal of PPIUCD.

Methodology: It is cross sectional study conducted from June 2019 to Dec. 2019 (six months) in Services Hospital, Lahore. We studied 2145 women who received PPIUCD during this period. The patients were called for follow up at 6 weeks and 6 months after insertion. The complication and complaints following insertion were recorded.

Results: About 39.3% of parturants this health facility accepted PPIUCD after counseling. Almost half of these patients presented for follow up at 6 weeks and 6 months. In this study 84.8% of women with PPIUCD were satisfied with this method. The reasons for IUCD removal included displaced IUCD followed by cramping pain (17.7%) and irregular vaginal bleeding (12.9%).

Conclusion: High level of satisfaction was observed in our study. Expulsion rate were low. Most of the problems/complaints were managed satisfactorily.

Key Words: Contraception, PPIUCD, Complications.

The postpartum period is one of the critical times when ovulation is highly unpredictable and couples often underestimate the likelihood of pregnancy. This exposes women to the risk of unintended pregnancy. Women presents with short inter pregnancy interval and high fertility rate contributing to high maternal and neonatal morbidity and mortality[(1)]. Appropriate provision of family planning services include antenatal and intrapartum counseling, support for initiating a method and postpartum guidance to successfully continue its use. Institutional deliveries create a unique opportunity to offer a long acting yet reversible method of contraception to women immediately following their childbirth. Delaying contraception until later is less effective because most clients tend not to return to health facilities for family planning services.

Pakistan is the sixth most populous country in the world with current population of 196 million and growth rate of 2.1%.[2] According to Pakistan demographic health survey (PDHS 2013), contraceptive prevalence rate (CPR) is 35% in which modern methods are only 26% and 20% of patients have an unmet need for family planning with 9% having unmet need for spacing and 11% having unmet need for limiting their family.[3] The reported prevalence of unintended pregnancies in Pakistan is 38-46%.[4]

The family planning programme was started in Pakistan in 1950 but its success rate had been limited. The hospital family planning Units were separate from most of maternity Units making it unfeasible for pregnant women to visit. According to vision of World Health Organization (WHO), postpartum family planning (PPFP) is now focusing on

1. Zahida Noreen
2. Robina Tariq
3. Aymen Javed
4. Alia Bashir

1-4. Department of Gynaecology, Services/SIMS Lahore

Correspondence:
Dr. Robina Tariq, Associate Professor of Gynaecology, SIMS, Lahore

Submission Date: 20-12-2020
1st Revision Date: 26-12-2020
Acceptance Date: 28-12-2020

prevention of unintended and closely spaced pregnancies through the postpartum contraception plan.[5] PPFP was first introduced in Pakistan in 2012 in collaboration with Jhpiego.

Postpartum intrauterine contraceptive device (PPIUCD) is the only family planning method which is highly effective, reliable, inexpensive, non - hormonal, immediately reversible and long acting contraceptive that can be initiated during the immediate postpartum period and it has no negative effects on lactation.[6-8] The initiation and provision of contraceptive methods during the immediate postpartum period safeguard the women from unintended pregnancy before they resume sexual activity or return to fecundity.[9] The insertion of immediate PPIUCD is safe and easy when compared with delayed postpartum and interval insertion of the intrauterine contraceptive device (IUCD)[10] and it can be initiated by mid-level birth attendant.[11]

Despite the family planning counseling and awareness regarding the PPIUCD and other effective methods, Pakistan is still lagging behinds achieving its desired contraceptive prevalence rate (CPR). Ignorance, lack of adequate knowledge and wrong beliefs and information are common hurdles responsible for failure to achieve our desired goals.

This study is conducted in Services Hospital Lahore, to determine the reasons behind removal of PPIUCD even before the completion of first year of insertion. The aim of the study is to identify the factors that are responsible for the failure of this highly effective method and ways to improve the acceptance of this method. We have focused on patient's satisfaction of this method and if not satisfied then to identify the reasons of unsatisfaction.

METHODOLOGY

The study was conducted at Services Hospital, Lahore, the Department of Obstetrics & Gynaecology. It was a prospective longitudinal study from June 2019 to Dec. 2019 (six months). After getting ethical approved from review board of Services Institute of Medical Sciences, data collection was done. Counseling of patients was done in antenatal, intrapartum or postpartum period regarding different methods of contraception, their advantages mode of action, complications and need for follow up. Acceptance for any of these methods was recorded in antenatal card/case record.

PPIUCD was inserted in women who gave written consent and had no contraindications for this method. It was inserted after delivery by SVD/ LSCS. The woman with anemia (Hb <8g/dl), premature rupture of membranes for more than 18 hours, postpartum haemorrhage, congenital malformation of the uterus and active infection of genital tract were excluded and they were counseled for other methods of postpartum contraception. PPIUCD insertion was done by residents who had been trained for this purpose. A record of all these insertion was maintained with residential addresses. After insertion of PPIUCD either in SVD or lower segment caesarean section, the women were given a card showing type and date of IUCD insertion with date of follow up at 6 weeks and then at 6 months respectively.

The follow up of the women was done in OPD or telephonically. The women were asked about any menstrual irregularity, vaginal discharge, abdominal cramp, or expulsion. The reasons for requesting removal of PPIUCD were also noted. In this way, data was collected at 6 weeks and 6 months. Data collection was performed using labour room record and follow up register for PPIUCD.

RESULTS

Table-1 describes the demographic characteristics of patients who were given PPIUCD (2145). These characteristic include age (years), parity, education, residence, economic status, fertility wishes and time of counseling regarding PPIUCD and if shows distribution of clients according to these characteristics.

Table-2 shows the total number of birth that occurred in Obs. & Gynae Department of Services Hospital, Lahore during the six months (from July 2019 - Dec. 2019). The numbers of births are des-

cribed separately according to mode of delivery i.e SVD, assisted or LSCS.

Table 1: Demographic Characteristics of Patients Who Accepted PPIUCD (2145)

Characteristics	Categories	Number (%)
Age (Year)	20-25	420 (19.6%)
	25-30	1024 (47.7%)
	> 30	701 (32.7%)
Parity	One	245 (11.4%)
	Two	765 (35.7%)
	Three	540 (25.2%)
	Four or more	595 (27.7%)
Education	Uneducated	561 (26.2%)
	High School	1112 (51.8%)
	Intermediate or above	472 (22%)
Residence	Rural	1060 (49.4%)
	Urban	1085 (50.6%)
Economical Status	Lower class (< 15k)	563 (26.3%)
	Low middle class (15k-30k)	1110 (51.7%)
	Upper middle class (>30k)	472 (22%)
Fertility Wishes	Yes	1481 (69%)
	No	664 (31%)
Counseling Regarding IUCD Insertion	Antenatal	472 (22%)
	Intrapartum	1024 (47.7)
	Postpartum	649 (30.3)

A total of 2145 (39.3%) clients accepted PPIUCD.

Table 2: Total Number of Births (n=5456)

Mode of Delivery	Total
SVD	2676
Assisted (Forceps/Vacuum/Breech)	22
LSCS	2758
TOTAL	5456

Table-3 Describes the distribution of PPIUCD clients according to the time of insertion of PPIUCD.

Table 3: Time of Insertion of PPIUCD (n=2145)

Route and Time of Insertion of PPIUCD	Total Number	Percentage
Within 10 min of SVD	1174	54.7%
Intra caesarean	968	45.1%
Immediate PP (within 48 hrs)	3	0.2%
Total	2145	100%

Table-5 Describe the complications/findings described by the clients at follow up visit after 6 weeks and at 6 months. Interestingly 1464 patients (68.2%) with PPIUCD could be followed up.

It was made sure that same patient was not counted twice if she showed for both follow up.

Table 4: Complications & Findings at Follow Up Visit

Complications/Findings at Follow Up Visit	After 6 weeks	6 Months Follow Up
No complaints	741 (50.6%)	500 (34.2%)
Side effects (bleeding & pain)	56 (3.8%)	44 (3%)
Expulsion	12 (0.8%)	4 (0.3%)
Displaced IUCD	16 (1.1%)	9 (0.6%)
Infection	1 (0.1%)	17 (1.2%)
Missing Strings	0 (0%)	2 (0.1%)
IUCD removal for different reasons	6 (0.4%)	56 (3.8%)

Table-6 Describe the common seasons for IUCD removal along with their percentages

Table 5: Common Reasons for IUCD Removal (n=62)

Common Reasons for IUCD Removal (Total No. 56)	No	%
Displaced IUCD	36	58.1%
Infection	7	11.3%
Side effects - Cramping	11	17.7%
Side effects - per vaginal spotting	8	12.9%

DISCUSSION

This study shows that the women who selected IUCD as postpartum contraception mostly belonged to low middle class and had received basic education. The most effective period for counseling regarding IUCD in antepartum and intrapartum period. Almost 39.3% (2146) of delivered patients gave consent for PPIUCD. This figure is higher as compared to (10%) in a previous study in the same health facility[12] and also from a study in Ethiopia showing an acceptance in 12.4% parturants.[13] Acceptance rate is higher in our study which may be due to ongoing training and campaign for PPIUCD. The percentage of women who opted for PPIUCD is higher (54.7%) after SVD as compared to women who underwent lower segment caesarean section (45.1%).

In our study 1464 (47.5%) of the women with PPIUCD were available for follow up. About 84.8% of these women did not report any complaint. This proves the effectiveness and safety of this method.

The common complaints e.g bleeding, pain, discharge and infection at follow up were easily addressed by symptomatic treatment. Women who were educated were more likely to convince their spouses about agreement on their decision to use PPIUCD. Having a higher level of education and financial security was significantly associated with accepting this reliable, long acting, coitus independent method. This finding concurs with a report from Pakistan indicating that contraceptive use was strongly associated with woman's education.[14] A possible rationale behind this connection is that the financial contribution made by women enables them to control certain decisions including their reproduction.[15]

Only 62 (2.9%) patients out of 2145 had their IUCD removed due to different reasons. The most common causes of IUCD removal include displaced IUCD (58.1%) followed by cramping (17.7%) and irregular vaginal bleeding (12.9%). A study from India shows that the request for removal of IUCD was seen in 5.9% of patient. Menstrual irregularity (5%), cramping pain (8%) and displaced IUCD (4%.) as the main causes for this request.[19]

In current study 84.8% women were willing to continue with the decision including high level of satisfaction. They were willing to recommend this method to others as well. This compares favourably with continuation rate reportedly from Karachi (84%)[16] Paraguay (91%),[17] Turkey (87.6%)[18] and India (96%)[19,20]

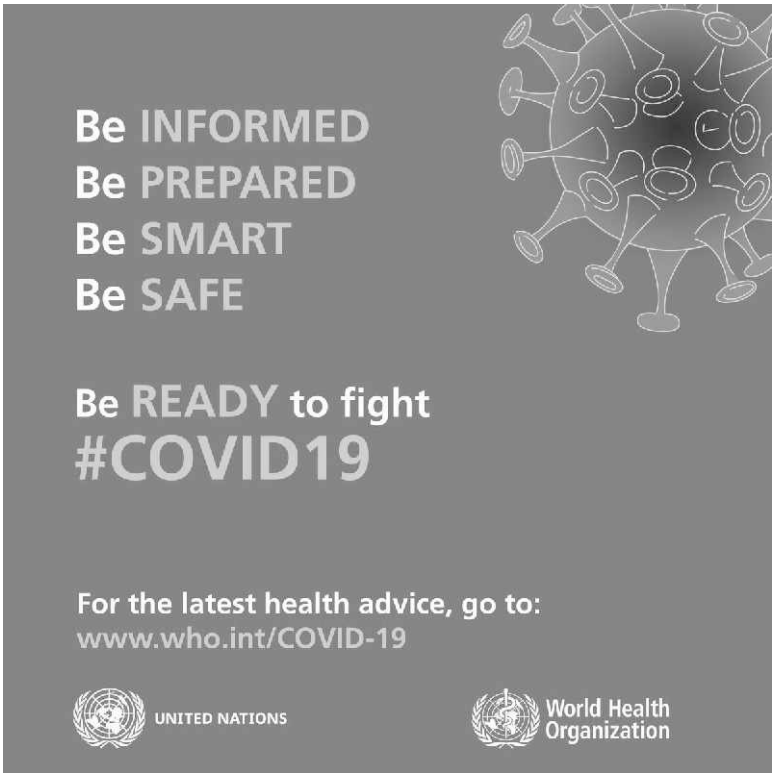
Our study includes a large sample of women with PPIUCD but the result cannot be generalized to whole country. The safety of this method has been highlighted in several stud ies. It can be used effectively for population control in under developed country. Education, financial empowerment of women and dedicated supportive staff for counseling and follow up of contraceptive services can ensure good results.

REFERENCES

1. Migninile ,Carreli G, Betran AP,et al;interpregnancy interval and perinatal outcomes across Latin America from 1990 to 2009: a large multi-country study. BJOG . 2010,123:730-737.
2. United Nations, Department of Economic and Social Affairs, Population Division (2015). World Population Prospects: The 2015 Revision, Key Findings and Advance Tables. Working Paper No. ESA/P/WP.241.
3. National Institute of Population Studies (NIPS) [Pakistan] and ICF International. 2013. Pakistan Demographic and Health Survey 2012-13. Islamabad, Pakistan, and Calverton, Maryland, USA: NIPS and ICF International.
4. Habib AM, Greenow RC, NausheenS, Soofi BS, SajidM, Bhutta AZ, et al. Prevalence and determinants of unintended pregnancies amongst women attending antenatal clinics in Pakistan. BMC Pregnancy and Childbirth 2017; 30: 17:156
5. World Health Organization. Programme strategies for post partum family planning. Geneva; WHO: 2012.http://www.mchip.et/sites/default/files/postpartum family planning.pdf. Accessed April 24, 2014.
6. WHO. Programming Strategies for Postpartum Family Planning; World Health Organization. Geneva: WHO Libr Cat Data; 2013. ISBN 978 9
7. Hounton S, et al. Patterns and trends of postpartum family planning in Ethiopia, Malawi, and Nigeria: evidence of missed opportunities for integration. Glob Heal Action. 2015;8:29738. doi.org/ 103402/gha. v829738
8. Jhpiego Corporation. Postpartum Intrauterine Contraceptive Device (PPIUD) Services; A Reference Manual for Providers. Balt Maryl 21231-3492, USA. ACCESS Family Planning Initiative, USIAD. 2010. https://www.glowm.com/pdf/Global%20PPIUD%20Reference%20Manual.pdf
9. Udgiri R, Sorganvi V. Knowledge attitude and practices of family planning methods among postnatal mothers-a hospital-based study. Al Ameen J Med Sci. 2016;9(2):134-8.
10. Canning D, Shah IH, Pearson E, Pradhan E, Karra M, Senderowicz L, et al. Institutionalizing postpartum intrauterine device (IUD) services in Sri Lanka, Tanzania, and Nepal: study protocol for a cluster-randomized steppedwedge trial. BMC Pregnancy Childbirth. 2016:1-11. Available from: http://dx.doi.org/10.1186/s12884-016-1160-0
11. Huffling K, Brubaker L, Nash-Mercado A, McKaing C. An Annotated Bibliography of Postpartum Family Planning Literature. ACCESS Fam Planning Initiative. April 2008. http://reprolineplus.org/ system/files/ resources/ppfp_bibliography_2008.pdf.
12. Noreen Rasool, Sofia Tabassum, Robina Sohail,

Safety and Acceptability of PPIUCD. Esculapsia - Vol.10, April-June 2014.

13. Alemyehu Gonie, Chanyalew Worku, Tesfaye Assefa, Daniel Bogale and Alemu Girma. Acceptability and factors associated with PPIUCD among women who gave birth at bale zone health facilities, south-east-Ethiopia. Contraception and reproductive medicine (2018)3:16.
14. Saleem S, Bobak M. Women's autonomy, education and contraception use in Pakistan: a national study. Reprod Health. 2005; 2(1):8. http://dx.doi.org/10.1186/1742-4755-2-8.
15. Dixan - Mueller R. The sexuality connection in reproduction Health. Study Fam Plann. 1993; 24(5): 269-82.http://dx.doi.org//0.2307.
16. Afshan A, Asim S. Immediae Postpartum IUCD (PPIUCD). Insertion: An opportunity Not to be missed. Ann Abbas: Shaheed hosp Karachi: Med Dent Coll;2014;19:15-20.
17. Araujovb, Oritz L, Smith J: Postpartum IUD in paraguary: A case series of 3000 cases. Contraception 2012;86:173-86.
18. SevKi Glen, Perran M, Ayhan Suak, Ayla Aktulay, Nuri Dan S. Clinical outcomes of early postplacental insertion of intrauterine contraceptive divices. Contraception.2004;69"279-82.
19. Kumar S, Sethi R, Balasubramaniam S, Chaniat E, Lalchandani K, Semba R, et al. Women's experience with postpartum intrauterine contraceptive device use in India. Reprod Health. 2014;11:32.
20. Fairaj S, Dayyabla S. A cross sectional study on Acceptability and Safety of IUCD among Postpartum Mother at fertiary care hospital, Telegana. J clin Diagn Res.2016;10: LCO1- LCO4.



ETIOLOGICAL SPECTRUM OF GLOMERULAR DISEASES AMONG PATIENTS PRESENTING WITH NEPHROTIC RANGE PROTEINURIA TO A TERTIARY CARE HOSPITAL IN LAHORE

Khurram Iftikhar,[1] Sidra Shafiq Cheema,[2] Shafiq ur Rehman Cheema[3]

How to cite: Iftikhar K, Cheema SS, Cheema SR. Etiological spectrum of glomerular diseases among patients presenting with nephritic range proteinuria to a tertiary care hospital in Lahore. JAIMC. 2021; 19(1): 221-228.

Abstract

Glomerular diseases encompass a group of renal diseases that usually presents with proteinuria. Histopathological analysis of the renal tissue helps in accurate diagnosis of the lesions and subsequent management.

Objectives: To determine the frequency of various types of glomerular diseases among patients presenting with nephrotic range proteinuria in a tertiary care hospital. Histopathological diagnosis of the renal biopsies and categorization into various common causes of glomerulonephritis. It was a cross-sectional study Six months from September 2018 to February 2019 at Nephrology Department/ Dialysis Center, Jinnah Hospital, Lahore.

Methodology: All patients underwent real time ultrasound guided percutaneous renal biopsy with core biopsy with automatic gun 16-18 G using standard protocol and the sample was sent to pathology laboratory for histopathology. Results were categorized into various histopathological types of common glomerular diseases.

Results: There were 205 patients in the study with mean age 44.5 ± 12.6 (range: 16 – 60) years with 110 (53.7%) males and 95 (46.3%) female patients. The mean body mass index of the patients was 19.6 ± 3.1 (range: 14 – 31) Kg/m2. Histopathological analysis revealed that 21 patients (10.2%) had minimal change disease, 78 (38.0%) had focal segmental glomerulosclerosis, 54 (26.3%) had membranous nephropathy, 25 (12.2%) had membranoproliferative glomerulonephritis, 18 (8.8%) had mesangioproliferative glomerulonephritis and 9 (4.5%) had lupus nephritis.

Conclusion: Glomerular diseases are highly prevalent in patients with proteinuria and focal segmental glomerulosclerosis is the commonest glomerulonephritis in patients with nephrotic range proteinuria.

Key Words: Proteinuria, glomerular diseases, frequency, incidence, histopathology, prevalence

Glomerular diseases (GD) are common in our as well as other countries of the world. They are associated with heavy burden of renal morbidity and mortality, and happen to be the leading cause of end stage renal disease (ESRD). In the absence of a natio-nal or regional renal biopsy registry, we lack the essential epidemiological data to formulate a compre-hensive plan to manage the glomerular diseases and their long-term sequelae. In our healthcare system of meagre resources and limited nephrology services, there is a dire need for ways and protocols whereby these diseases can be detected and managed early. Proteinuria being the hallmark of glomerular disease can be utilized as one basic laboratory parameter that is readily detectable on a urine dipstick test and can prompt a further investigation into the diagnosis of a possible glomerular disease.[1]

Importance of timely urinalysis in managing glomerular disease cannot be over emphasized.[2] Similar is the utility and cost-effectiveness of pro-

1. Khurram Iftikhar
2. Sidra shafiq Cheema
3. Shafiq ur Rehman Cheema

1. Jinnah Hospital, Department of Nephrology
2. Department of Pathology,CMH Lahore Medical College
3. Professor & Head of Nephrology, Jinnah Hospital,Allama Iqbal Medical College, Lahore

Correspondence:
Dr. Khurram Iftikhar, *Jinnah Hospital, Department of Nephrology*

Submission Date: 24-12-2020
1st Revision Date: 28-12-2020
Acceptance Date: 29-12-2020

teinuria screening in an emerging country like ours. Proteinuria is a marker of kidney disease, and it plays a role in screening, diagnosis, and monitoring. It is also an independent risk factor for cardiovascular events and progressive kidney disease.[3]

Nephrotic-range proteinuria is absolutely characteristic of glomerular disease. Asymptomatic proteinuria is much less specific and may occur with a wide range of renal and urinary tract conditions that must be excluded by clinical evaluation and investigation. As physiologic proteinuria does not exceed 150 mg/24hrsfor adults and 140 mg/m^2 for children, the fact remains that significant proteinuria will most commonly be seen in association with glomerular disease.[4] Glomerular diseases generally present with variable degree of proteinuria, hematuria, hypertension,impaired renal function or ESRD. It can present as nephrotic syndrome (NS), nephritic syndrome, rapidly progressive glomerulonephritis (RPGN), acute kidney injury (AKI), chronic kidney disease (CKD), macroscopic hematuria (MH), as well as isolated proteinuria or hematuria. Clinical presentation of glomerular disease may not essentially confirm to a given morphological glomerular disease.[5] That is why the diagnosis of glomerulopathies requires a close cooperation between clinicians and pathologists. Renal biopsy plays fundamental role in the evaluation of proteinuric patients, their treatment and to assess prognosis. Since its introduction into clinical usage in the early 1950's, percutaneous renal biopsy is one of the most common and widely accepted invasive procedures for the diagnosis of renal diseases. It is safe, easy and convenient to perform, and has high diagnostic yield with few complications. Although immunofluorescence and electron microscopy have important role in the study of renal pathology most of the glomerular diseses can still be diagnosed by light microscopy with reproducibility.[6] The incidence of glomerular diseases varies according to the population characteristics, environmental factors, socioeconomics and prevalence of infectious diseases. In addition, the incidence varies according to the detection level of urinary findings, the biopsy resources of the community and the biopsy policy whether liberal or strict.As not all patients with renal disease are biopsied, the rate of biopsy-proven renal diseases underestimates their true prevalence. The incidence rates vary in different countries. Changing incidence of glomerular diseases over time has been noted in different communities possibly due to genetic and environmental factors.[7] Since renal biopsy has a pivotal role in the assessment and management of proteinuric patients therefore we aimed to determine the histopathological pattern of glomerular lesion by percutaneous renal biopsy in proteinuric patients in our study.

The various types of glomerular diseases associated with nephrotic range proteinuria[3] show considerable variation in their frequencies. A study conducted in Sudan showed FSGS as the most common pattern with a frequency of 29.6% followed by MPGN 26.8% and MCD 16.9% while MesPGN was the predominant histological pattern 21.1% in a study conducted in Nepal followed by MPGN 18.6% and MN 14.2%. Another Indian based study showed highest frequency of 26.5% for minimal change disease with FSGS 13.2% and MN 18.8%.

A study was conducted in Pakistan with an aim to determine the histological pattern in renal diseases. It revealed FSGS as the most common variant with 28% frequency while MN, MCD, MPGN and lupus nephritis present in a frequency of 14%, 12.5%, 10% and 7% respectively. Another study done in single Chinese center showed highest frequency of idiopathic membranous nephropathy (IMN) 20.7% followed by minimal change disease 20.4%, this study also categorized patient on basis of age and sex and included patients with nephrotic syndrome. But it lacks information specifically as which is more commonly involved in causing nephrotic range proteinuria.

The rationale of this study was to determine the histological spectrum of the glomerular diseases among patients of nephrotic range proteinuria presenting to nephrology department or tertiary care

hospital. The existing literature showed considerable variation in the frequency of glomerular diseases so this study aims to further determine the common histological disease underlying nephrotic range proteinuria. The management and prognosis of each glomerular disease is different and dependent upon renal biopsy but the availability of this facility is limited to a few set-ups only. Thus, these results would help the clinicians to start evidence based empirical treatment especially in settings where there is no facility of renal biopsy or patients are not willing for biopsy so that they can be managed timely to improve the prognosis.

METHODOLOGY

Study Design: Cross sectional study

Duration of Study: Six months after approval of synopsis from August 2018 to February 2019.

Settings: The study was conducted in Nephrology Department of Jinnah Hospital, Lahore

Sample Selection: Patients were selected following the below mentioned criteria.

Inclusion Criteria:

- Age 15 to 60 years
- Both gender
- Patients presenting with nephrotic range proteinuria to the nephrology department of a tertiary care hospital

Exclusion Criteria:

- Patients not willing to participate in the study
- Patient with uncontrolled hypertension (BP > 150/ 100 mm Hg) determined by the blood pressure measurement by sphygmomanometer despite maximum tolerated anti-hypertensive medications.
- Patient with solitary functioning kidney
- Patients with abnormal coagulation profile i.e. PT >13 sec, APTT > 34 sec, platelets <100,000, BT > 2 minutes.

A sample size of 205 cases was calculated with 95% confidence level, 3.5% margin of error and taking expected percentage of lupus nephritis in patient with glomerulonepritis as 7% (least among all) (85). Sampling Technique was non probability consecutive sampling.

A total of 2015 patients presenting with nephrotic range proteinuria to the Nephrology Department of Jinnah Hospital Lahore and fulfilling the inclusion criteria were approached. An informed consent was taken from them before enrolling in the study. Information regarding their school demographic data were noted in the perform. All patients underwent real time ultrasound guided percutaneous renal biopsy with core biopsy automatic gun 16-18 G using standard protocol and the sample was sent to pathology laboratory for histopathology by the researcher himself. Patient was closely monitored during next 24 hours for possible procedure related complications in Nephrology Department JHL. The report was collected by the researcher and the results were noted in the Proforma ensuring patient confidentiality. Types of glomerular diseases were labeled as per operational definitions.

Data were entered and analyzed using SPSS version 21.0. Numerical variable i.e. age were summarized as mean and standard deviation. Qualitative variables like sex and type of glomerulonepritis were presented in the form of frequency and percentages. Data were stratified for age, gender, BMI and Chi-square test was used to check statistical significance post-stratification. A p-value < 0.05 was considered statistically significant.

RESULTS

There were 205 patients in the study with mean age 44.5 ± 12.6 (range: 16 – 60) years. We divided the patients into 3 groups of equal age ranges. The maximum number of patients were found in the age group 31 – 45 years with 102 (49.8%) patients falling in this age group (Table 1, Figure 1). There were 110 (53.7%) males and 95 (46.3%) female patients in the study with female to male ratio being 1:1.16 (Table 2, Figure 2). The differences in the ages of the male and female patients was statistically not significant.

We divided the patients on the basis of body

mass index. We found out that maximum number of patients (81, 39.5%) had body mass index ranging from 18.5 – 24.9 Kg/m^2. The mean body mass index of the patietns was 19.6 ± 3.1 (range: 14 – 31) Kg/m^2 (Table 3, Figure 3). Stratification of study population on the basis of spot urinary protein to creatinine ratio revealed that 108 patients (52.7%) had spot urinary protein to creatinine ratio ranging from 2.0 – 2.5, 74 (36.1%) had ratio from 2.6 – 3.0 and 23 (11.2%) had ratio greater than 3.0 (Table 4, Figure 4).

Analaysis of various histopathological types of glomerular diseases in our study population revealed that 21 patients (10.2%) had minimal change disease, 78(38.0%) had focal segmental glomerulosclerosis, 54 (26.3%) had membranous nephrotpathy, 25 (12.2%) had membranoproliferative glomerulonephritis, 18(8.8%) had mesangioproliferative glomerulonephritis and 9 (4.5%) had lupus nephritis. The commonest glomerunephritis was focail segmental glomerulonephritis that was found in 78 (38.0%) patients (Table 5, Figure 5). In order of decreasing frequency, our study showed following pattern: focal segmental glomerulosclerosis > membranous nephropathy > membranoproliferative glomerulonephritis > minimal change disease > mesangioproliferative glomerulonephritis > lupus nephritis.

We stratified patients on the basis of age, gender, body mass index and spot urinary protein to creatinine ratio. We found out that all the histopathological patterns of disease did not show any statistically significant relationship with age (p-value > 0.05) (Table 6). However, we observed that when stratified with regards to gender, lupus nephritis occurred more frequently in females as compared to males (p-value=0.001) (Table 7). All the rest of the glomerular diseases did not show any statistically significant relationship with gender (p-value > 0.05) (Table 7).

We also observed that focal segmental glomerusclerosis occurred more commonly in patients with body mass index in lower ranges but the observation was statistically not significant (p-value = 0.642). Majority of the patients with proteinuric glomerulonephritis fell in the body mass index ranging from 18.5 – 24.9 Kg/m^2 (Table 8) except for aforementioned focal segmental glomerulosclerosis which occurred most frequently in patients with body mass index less than 18.5 Kg/m^2 (Table 8).

Analyzing the relationship between spot urinary protein to creatinine ratio with various histopathological types of glomerular diseases, our study showed that majority of the patients with focal segmental glomerulosclerosis (n=43, 55.1%) had spot urinary protien to creatinine ratio ranging from 3.5–4.0 mg/mg and this observation was statistically significant (p-value=0.054). Similarly, majority of the patients with mesangioproliferative glomerulonephritis (n=13, 72.2%) had spot urinary protein to creatinine ratio ranging from 2.6 – 3.0 (p-value= 0.017). Findings of the rest of the relationships between spot urinary protein to creatinine ratio with types of glomerular diseases were not statistically significant (p-value > 0.05) (Table 9).

DISCUSSION

This study highlights a high incidence of glomerular diseases as well as a diverse histopathological pattern in patients having proteinuria on presentation. This cohort of proteinuric patients was selected from all our patients undergoing renal biopsy for various indications. The study population is a heterogeneousone in terms of demographic data as our hospital receives patients from all over the province as well as other parts of the country. There exist several biases including socioeconomic, geographical, climatic and racial characteristics (8-11). However the strengths of our study were our liberal biopsy policy, and the uniform protocols for biopsy indications, analysis of clinical syndromes and the histopathological evaluation of biopsy. Results of this report cannot be generalized and it cannot by any means be representative of a national epidemiological study of the biopsy-proven renal diseases. The incidence of glomerular diseases varies according to the biopsy resources and biopsy

policies. These are reflected in the histological diagnoses that are made. There is no universally valid "epidemiology" of glomerular disease[12]. Some centers only take biopsies when the pathological diagnosis would affect the therapy, or in subjects with signs of progressive renal disease. Many differences in specific proportions (or incidence) of glomerulopathies can probably be explained by these confounding factors. In our center, renal biopsy is carried out on patients with any sign of renal dysfunction or proteinuria of any level. Nonetheless, among patients with hematuria alone, many nephrologists do not undertake renal biopsy. This may be a reason for the high incidence in our database of focal segmental glomerular disease.

Male predominance was obvious in our study except in the case of lupus nephritis that was seen exclusively in females. This reflects the increased prevalence of lupus nephritis in the female population. All recently published studies worldwide show a similar pattern.[13] Focal segmental glomerulosclerosis (FSGS) was the commonest of all glomerular diseases as well as the most common cause of nephrotic syndrome in our study. This is in agreement with many studies reported from our region and other countries. A worldwide increase has been noted in the incidence of FSGS despite racial variations. There are no data available on true incidence of glomerular diseases in Pakistan and there have been conflicting reports from Pakistani studies whether our data of various glomerulonephitis incidences coincides with that from other countries. Reason for this discrepancy may be the fact that some centers have strict biopsy criteria and obtain a biopsy only when the pathology would alter the therapy while other centers have liberal biopsy policy and try to establish an early specific diagnosis, whenever there is evidence of kidney disease on urinalysis. Although our data may not be a true reflection of the histopathological pattern of renal diseases in our region, this study fulfils the purpose of our objective as well as highlights usefulness of proteinuria screening for diagnosing glomerular diseases. A proactive approach is required for identification of glomerular diseases especially in patients harboring a risk factor like proteinuria. Provision of optimum diagnostic facilities at hospitals, and establishment of a national renal biopsy registry are recommended to know the true incidence of glomerular diseases. Collection of data relating to renal biopsies in a national registry is a useful tool for nephrologists in that it will allow epidemiologic studies for both prevention and treatment of renal diseases

Focal segmental glomerulosclerosis turned out to be the commonest glomerular disease in our study population. FSGS is a condition of unknown origin and pathogenesis. In recent years, it has been suggested that FSGS is not a single clinicopathological entity but represents a heterogenous group of disease in which focal and segmented glomerular sclerosis is the common denominator. Some authors have attempted to subdivide FSGS into specific subgroups based on such features as size of the glo-

Table 1: *Age Distribution of Study Population in Different Age Groups*

Age Groups (Years)	Number of Subjects (n = 205)	Percentage (%)
15 – 30	41	20.0
31 – 45	102	49.8
45 – 60	62	30.2
Total	205	100.0

(Mean Age: 44.5 ± 12.6 years) (Range: 16 – 60 years)

Table 2: *Gender Distribution of Study Population*

Gender	Number (n)	Percentage (%)
Male	110	53.7
Female	95	46.3
Total	205	100.0

(Female : Male :: 1 :1.16)

Table 3: *Distribution of Patients According to Body Mass Index*

Body Mass Index (BMI in Kg/m^2)	Number of patients (n)	Percentage (%)
< 18.5	64	31.2
18.5 – 24.9	81	39.5
25 – 29.9	52	25.4
⩾	8	3.9
Total	205	100.0

Mean BMI: 19.6 ± 3.1 Kg/m^2 Range: 14 – 31 Kg/m^2

mernlus and location of the segmented sclerosis within the glomeruli. For example, cases of FSGS with sclerosis limited to the tubular pole of the glomerulus (tip lesion) are thought to belong to a specific entity with excellent prognosis. Another lesion is characterized by enlarged glomerular size and lesions of sclerosis primarily limited to the vascular pole. This is typically associated with reduced renal mass and has been suggested as a specific subgroup of FSGS. Others, however, have argued that these features are not sufficiently consistent and reproducible to warrant specific subcategorization of FSGS lesions.

In the current study, no attempt was made to distinguish between various subgroups of FSGS.

Table 4: *Spot Urinary Protien to Creatinine Ratio in Study Population*

Spot Urinary Protien to Creatinine Ratio	Number (n)	Percentage (%)
3.5 – 4.0	108	52.7
4.1 – 5.0	74	36.1
> 5.0	23	11.2
Total	205	100.0

The diagnosis of FSGS in our cases was based on the demonstration of classical lesions characterized by collapse of capillaries with sclerosis and capsular synenchae.[14-15] None of our biopsy specimens showed features of collapsing glomerulopathy as described by another study.[16] Why the frequency of primary FSGS should be so high in this series is not very clear. Histologically, the distinction between minimal change disease (MCD) and FSGS in its early stage is not easy, and FSGS could be misdiagnosed as minimal change disease. This may explain in part the relatively high frequency of MCD that has been reported in some local series, because some cases of FSGS might have been classified as MCD.[11]

Furthermore, the time at which the renal biopsy is performed is also said to be critical for the histological classification of glomerular disease, with minimal changes occurring more frequently in areas where the renal biopsy policy is performed early and

Table 5: *Frequency of Various Histopathological Types of Glomerular Diseases in Protienuric Patients*

Type of Glomerulonephritis	Number (n)	Percentage (%)
Minimal Change Disease	21	10.2
Focal Segmental Glomerulosclerosis	78	38.0
Membranous Nephropathy	54	26.3
Membranoproliferative Glomerulonephritis	25	12.2
Mesangioproliferative Glomerulonephritis	18	8.8
Lupus Nephritis	9	4.5
Total	**205**	**100.0**

vice versa. Therefore, the discrepancy between local centers in the reported frequencies of FSGS might have been influenced by the referral pattern and renal biopsy policy. Until further studies are carried out and methods are standardized, it is not possible to determine whether the disease pattern seen in this study is truly representative of that seen in the population. But overall, the study does highlight frequencies of various histopathological types of glomerular diseases in patients with proteinuria. So, the primary objective of the study was successfully met and we believe our study will enlighten the nephrologists about epidemiology and frequencies of various glomerular diseases in our country in a very nice fashion.

CONCLUSION

Glomerular diseases are highly prevalent in patients with proteinuria. The major histopathological types of glomerular diseases in our population turned out to be focal segmental glomerulosclerosis > membranous nephropathy > membranoproliferative glomerulonephritis > minimal change disease > mesangioproliferative glomerulonephritis > lupus nephritis in order of decreasing frequencies. Our study findings are analogous to recently reported United states and westeren literature.

Table 6: *Effect Of Age On Various Histopathological Types Of Glomerular Diseases In Proteinuric Patients*

Type of Glomerulonephritis	Age Groups (years)			Number (n)	P-value
	15–30	31–45	46–60		
Minimal Change Disease	3	12	6	21	0.531
Focal Segmental Glomerulosclerosis	20	35	23	78	0.641
Membranous Nephropathy	8	30	16	54	0.712
Membranoproliferative Glomerulonephritis	5	12	8	25	0.512
Mesangioproliferative Glomerulonephritis	2	10	6	18	0.431
Lupus Nephritis	3	3	3	9	0.31
Total	**41**	**102**	**62**	**205**	

Table 7: *Effect Of Gender On Various Histopathological Types Of Glomerular Diseases In Proteinuric Patients*

Type of Glomerulonephritis	Male	Female	Total	p-value
Minimal Change Disease	10	11	21	0.532
Focal Segmental Glomerulosclerosis	45	33	78	0.631
Membranous Nephropathy	30	24	54	0.654
Membranoproliferative Glomerulonephritis	12	13	25	0.312
Mesangioproliferative Glomerulonephritis	12	6	18	0.071
Lupus Nephritis	1	8	9	**0.001**
Total	**110**	**95**	**205**	

Table 8: *Relationship Between Body Mass Index And Various Histopathological Types Of Glomerulonephritis*

Type of Glomerulonephritis	Body Mass Index (Kg/m^2)				Number (n)	p-value
	< 18.5–24.9	18.5–24.9	25.0–29.9	30		
Minimal Change Disease	10	5	4	2	21	0.523
Focal Segmental Glomerulosclerosis	33	28	15	2	78	0.642
Membranous Nephropathy	9	25	18	2	54	0.511
Membranoproliferative Glomerulonephritis	7	13	4	1	25	0.412
Mesangioproliferative Glomerulonephritis	4	6	8	0	18	0.337
Lupus Nephritis	1	4	3	1	9	0.424
Total	**64**	**81**	**52**	**8**	**205**	

Table 9: *Relationship Between Spot Urinary Protein To Creatinine Ratio And Various Types Of Glomerulonephritis*

Type of Glomerulonephritis	Spot Urinary Protien: Creatinine Ratio			Number (n)	p-value
	3.5 – 4.0	4.1 – 5.0	> 5.0		
Minimal Change Disease	10	7	4	21	0.623
Focal Segmental Glomerulosclerosis	43	25	10	78	**0.054**
Membranous Nephropathy	32	18	4	54	0.713
Membranoproliferative Glomerulonephritis	13	9	3	25	0.651
Mesangioproliferative Glomerulonephritis	4	13	1	18	**0.017**
Lupus Nephritis	6	2	1	9	0.649
Total	**108**	**74**	**23**	**205**	

REFERENCES

1. Akilesh S. Glomerular Disease. In: Pathobiology of Human Disease: A Dynamic Encyclopedia of Disease Mechanisms. 2014.
2. Khanam A, Rashid HU. Effect of spirulina on lipid profile in patients with glomerulonephritis. Bangladesh Ren J. 2001;
3. Kogon AJ, Pierce CB, Cox C, Brady TM, Mitsnefes MM, Warady BA, et al. Nephrotic-range proteinuria is strongly associated with poor blood pressure control in pediatric chronic kidney disease. Kidney Int. 2014;
4. Vachek J, Zakiyanov O, Tesar V. Proteinuria. Interni Medicina pro Praxi. 2018.
5. Knapp MS, Walker WHC. Glomerular Filtration Rate. British Medical Journal. 1967.
6. Webster AC, Nagler E V., Morton RL, Masson P. Chronic Kidney Disease. The Lancet. 2017.
7. De Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation. 2004;
8. Fournier T, Medjoubi-N N, Porquet D. Alpha-1-acid glycoprotein. Biochimica et Biophysica Acta - Protein Structure and Molecular Enzymology. 2000.
9. Hellman NE, Gitlin JD. Ceruloplasmin metabolism and function. Annu Rev Plant Physiol Plant Mol Biol. 2002;
10. Flower DR. The lipocalin protein family: structure and function. Biochem J. 1996;
11. Ikram M, Muhammad S, Ali A, Muhammad N, Bahadur K, Haq MIU. Frequency of Histo-

pathological Patterns of Renal Diseases in a Tertiary Care Hospital. J Postgrad Med Inst. 2017;31(2).

12. Drosos G, Ampatzidou F, Sarafidis P, Karaiskos T, Madesis A, Boutou AK. Serum Creatinine and Chronic Kidney Disease-Epidemiology Estimated Glomerular Filtration Rate: Independent Predictors of Renal Replacement Therapy following Cardiac Surgery. Am J Nephrol. 2018;48(2):108–17.
13. Rani AA, Viswanathan V. Estimated Glomerular Filtration Rate Using Creatinine-Based Chronic Kidney Disease Epidemiology Collaboration Equation. Indian J Nephrol. 2018;28(6):492–3.
14. Joardar S, Chatterjee R, Das S, Mani S. Focal Segmental Glomerulosclerosis as the Leading Cause of Idiopathic Nephrotic Syndrome: A different spectrum revealed by mandatory renal biopsy in all patients. Sri Lanka J Child Heal. 2016;45(2).
15. Singh T, Astor B, Zhong W, Mandelbrot D, Djamali A, Panzer S. Kidney transplant recipients with primary membranous glomerulonephritis have a higher risk of acute rejection compared with other primary glomerulonephritides. Transplant direct. 2017; 3(11).
16. Tsuchimoto A, Matsukuma Y, Ueki K, Tanaka S, Masutani K, Nakagawa K, et al. Utility of Columbia classification in focal segmental glomerulosclerosis: renal prognosis and treatment response among the pathological variants. Nephrol Dial Transplant. 2019;

INTERNAL CONSISTENCY AND VALIDITY OF SHORT SMOKING CONSEQUENCES QUESTIONNAIRE (SSCQ) AMONG UNIVERSITY STUDENTS

Mamoon Akbar Qureshi,[1] Momina Iftikhar,[2] Shajeel Akhtar[3]

How to cite: Qureshi MA, Iftikhar M, Akhtar S. Internal consistency and validity of short smoking consequences questionnaire (SSCQ) among university students. JAIMC. 2021; 19(1): 229-234.

Abstract

Background: As cigarettes have become more accessible to the general public, so has the prevalence of smoking increased in our society. Globally 36% for males and 9% for females among the ages group of 18-25 year olds smoke tobacco. In the course of substance abuse, there is a significant role of substance use outcome-expectancies i.e. the positive and negative consequences of drug use. In order to completely comprehend the epidemic of smoking, this physiological basis of smoking must be analyzed and for that a smoking consequences questionnaire was developed by Brandon and Baker in 1991.

Objectives: The objective of this study was to examine the internal consistency of Short Smoking Consequence Questionnaire (SSCQ) among university students.

Methodology: A Cross sectional Study was designed to assess outcome expectancies among university student at university of Punjab duration of study was from June 2016 to October 2017. SSCQ was administered to them in a private and confidential setting. Data was entered in SPSS version 21.0. Internal consistency and validity of the scales was evaluated by determining cutoff values and calculating Cronbach's alphas for all the four latent variables.

Results: Internal consistency was measured for all the four factors with Crohbach's Alpha for Positive reinforcement scale (PR) was .815 Appetite and weight control (AWC) was .837 ($0.9 > \alpha \geq 0.8$=Good) and for Negative reinforcement scale (NR) was .911, Negative consequences scale (NC) was .944 ($\alpha \geq 0.9$ = Excellent).

Conclusion: The study concluded that S-SCQ had good to excellent internal consistency and reliability. S-SCQ is valid tool that can be used to assess smoking outcome expectancies among Pakistani adolescent and young population.

Key Words: Outcome expectancies, smoking consequences, SSCQ, university students, smoking.

Smoking is the biggest avoidable risk factor as considered by World Health Organization. Toba-cco consumption is an important health hazards and it results into an array of diseases. The magnitudes of these diseases are far more grievous than those origi-nating from other substances that are used as recrea-tional drugs. Majority of these smokers have been through numerous unsuccessful attempts of absti-nence. Globally 36% for males and 9% for females among the ages group of 18-25 year olds smoke tobacco similar situation exist in Pakistan.[1,2,3]

Outcome expectancies regarding drugs in general are theorized as individual perception about their outcome both positive as well as negative in course of experimenting with that specific drug. These outcome expectancies are usually built in as significant

1. Mamoon Akbar Qureshi 2. Momina Iftikhar
3. Shajeel Akhtar
1,2. Department of Community Medicine, Allama Iqbal Medical and Dental College Lahore
3. Punjab Social Security Health Management Company, Raiwind Lahore.

Correspondence:
Dr. Mamoon Akbar Qureshi, *Department of Community Medicine, Allama Iqbal Medical and Dental College Lahore,*
E-mail: maq90@hotmail.com

Submission Date: 11-11-2020
1st Revision Date: 18-11-2020
Acceptance Date: 25-11-2020

hypothetical models for addiction and have significant motivational influences for drug use.[4,5]

In course of substance use and abuse these outcome expectancies have played a significant role in outcome of that particular substance abuse.[6,7] Models based on social learning theory for addiction behaviors postulates regarding these expectancies that they facilitate an association with more distant aspects like affective states, personality traits, and behavior that influence substance use.[8]

Support for this hypothesized characteristic of these outcome expectancies for drug addiction has been mainly formulated from similar studies on alcohol dependence. These outcome expectancies are main concept in addiction models. Many outcome expectancies that are related to cigarette smoking have been well recognized and many research findings advocate that specific outcome expectancies are associated with significant characteristics in cigarette smoking for example, dependence on nicotine, severity of smoking and smoking cessation attempts.[9,10]

In order to completely comprehend the epidemic of smoking, the physiological basis of smoking must be analyzed and for that by Brandon and Baker developed a 55 items smoking consequences questionnaire later a short version of this instrument was also made and was a reasonable substitute of this 55-item SCQA to appraise outcome expectancies for smoking in adult who smoked heavily. This questionnaire was a condensed version of the original SCQA.[11] Schleidcher et al in his study evaluated the modified version of this SSCQA questionnaire to inquire about multiple aspects of smoking. In this study he developed a questionnaire to furnish evidence on different variables that can inspire an adolescent to indulge in smoking.[11,12]

Brandon (1994) & Borreli (1996) found out that the negative affect augment the stronger expectancy for the negative affect reduction and risk of relapse and is well forecasted both in risk of relapse and severity of withdrawal. In contrast negative consequences outcome expectancy such as risk to health are theorized to be associated negatively with withdrawal severity after a duration as there is little chance the relapse will start smoking again if they anticipate suffering from grave health outcomes due to their smoking.[13] These findings are also supported by findings in other studies on expectancies for negative consequences as predictor of successful cessation. In specific the strong beliefs dealing with the negative smoking consequences are related negatively with relapse of drug addiction.[14]

Researches on smoking focus on health related aspects of smoking has been clearly recognized, but it cannot be said in the case of physiological aspects especially in university or college students in Pakistan. The study focused on university students who are smokers in order to get a deeper understanding on the psychological viewpoint of smoking and to assess internal validity and reliability of SSQ-A in our population. The usefulness of the outcome of this study in predicting smoking intervention outcomes among youth that are currently going on may be explored in future research.

METHODOLOGY

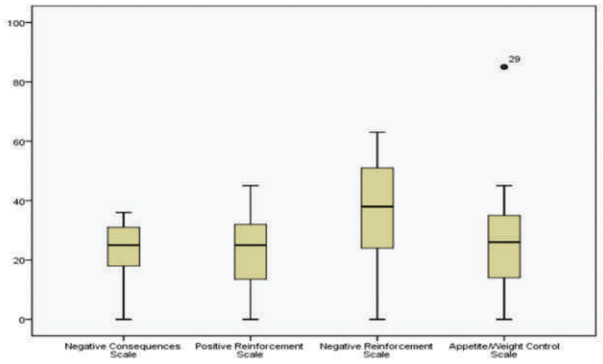
A Cross sectional study was designed to evaluate the internal validity and factor structure of smoking consequence questionnaire among university student. The study was conducted on adolescent group of student at University of Punjab from June 2016 – November 2016. A Non probability / purposive sample was size was calculated from university students fulfilling the following inclusion criteria of being a Regular / full time university students that are smokers using software win-pepi ver:11.15 to estimate a proportion with confidence level of 95% and acceptable difference of 0.05 with assumed internal consistency of 0.79. The required sample in study was 255. The short smoking consequence questionnaire (S- SCQ) was administered to them in a private and confidential setting. Female university students those who don't want to disclose their smoking habits were given in a closed envelope to maintain anonymity. Data was entered in SPSS

version 21.0. Mean standard deviation was calculated for numerical variables like age, number of cigarettes smoked and four factor analysis for Positive (PR) and Negative (NR) reinforcement, Negative consequences (NR) and Appetite and weight control (APW) was done. Validity and reliability was analyzed by defining cutoff values and calculating Cronbach's alphas for four factors individually and also for 21 item S-SCQ. Approval from ethical review board was sorted prior to conduction of study. Informed consent was taken prior to data collection and all the respondents were informed about research purpose and its outcome. Confidentially was maintained at all times during research.

RESULTS

255 respondents were given S-SCQ. Mean age of responded was 20.5922 SD+1.854 with minimum age of 18 years and a maximum of 24 years.90.2 % were male and 9.8% were female. (Graph no: 1). Mean duration of smoking was 3 years SD + 1.99 years with minimum duration was 6 months and maximum duration was 10 years. 79.2% were smoking for less than 5 years and 20.8% were smoking for 5-10 years. (Table no: 1).

For four factor reliability analysis mean score for Negative consequences scale (NC) was 23.43 SD + 9.638. Mean score for Positive reinforcement scale was 23.07 SD ± 12.937. Mean score for Negative reinforcement scale was 35.84 SD ± 18.197. Mean score for Appetite and weight control was 12.934 SD ± 9. (Graph no: 1).



Graph no: 1 *Mean Statistics of Four Factors in Short Smoking Consequences Questionnaire (SSCQ)*

Reliability Statistics for these four factors SSQ Crohbach's Alpha of .995 and Crohbach's Alpha Based on Standardized Items .891 with a item means 26.707 and minimum score of 23.071 and 35.843 and a variance of 37.457.

Factors	Negative Consequences (NC)	Positive Reinforcement (PR)	Negative Reinforcement (NR)	Appetite/ Weight Control (AWC)
Mean	23.43	23.07	35.84	24.48
Std. Deviation	9.638	12.937	18.197	12.934

Internal consistency was measured for all the four factors with Crobach's Alpha for Positive rein-

Table 1: *Demographic and Smoking Characteristics of Respondents (n=255)*

Variable	Frequency	Percent	Mean SD
Age of respondents			Mean =20.522 SD =± 1.85454
18 - 21 years	167	65.5	
21 - 24 years	88	34.5	
Gender of respondents			
Male	230	90.2	
Female	25	9.8	
Smoking status			
Smoker	218	85.5	
Ex-Smoker	37	14.5	
Duration of smoking			Mean = 3.0176 years SD = ±1.99524
< 5 years	202	79.2	
5 - 10 years	53	20.8	

Table 2: *Individual Reliability Statistics for Four factors in Short Smoking Consequences Questionnaire (SSCQ)*

Factors	Cronbach's Alpha	N
Overall SSCQ	.995	21
Negative Consequences(NC) (Items: 11, 15, 18, and 21)	.815	4
Positive Reinforcement(PR) (Items: 1, 4, 8, 9, and 10)	.911	5
Negative Reinforcement (NR) (Items: 3, 5, 7, 12, 14, 19, 20)	.944	7
Appetite/Weight Control(APW) (Items: 2, 6, 13, 16, and 17)	.837	5

forcement scale (PR) was .815 Appetite and weight control (AWC) was .837 (0.9 > α ≥ 0.8 = Good) and for Negative reinforcement scale (NR) was .911, Nega-tive consequences scale (NC) was .944 (α ≥0.9 = Excellent). (Table no: 2).

DISCUSSION

This study explored the validity and internal consistency of short version of smoking consequences questionnaire (SSCQ) in a university sample of young adult and adolescent in a public sector university. Until recently, outcome expectancies for cigarettes smoking have given considerably less consideration. Much of the research on cigarette smoking related perceptions has been done primarily with focus on belief, attitudes and underlying caused for smoking tobacco instead on expectancies for smoking. Moreover a considerable percentage of these researches have been done with methods that were not standardized for perceptions regarding smoking. Among these very few researches that have examined outcome expectancies for cigarette smoking with validating measures, that has been conducted among young adults that are college going.[13-15]

The validity of the SCQ among adult smokers has been evaluated in many studies. In a clinical trial for efficacy of the nicotine replacement in cessation treatment established that the original SCQ with a four factors is a valid instrument.[14] The predictive validity and utility of the four factors SCQ showed that these outcome expectancies measurements were related significantly to in evaluation of cessation of smoking and also in withdrawal but was unable to establish its validity among nicotine dependent subjects.

Myers (2003) conducted a research in order to build and confirm an abridged version of this 50 items questionnaire (SCQ) initially formed by Brandon. In the first study he used a short form of 21 items questionnaire (S-SCQ) which was developed from a subset of adolescent who were receiving treatment for drug addiction. My study is also an attempt to furnish an initial account for using this instrument in Pakistani adolescents' smokers and ex- smokers for outcome expectancies evaluation. Myers et al first study exhibited the validity and reliability among adolescent and young adults for SSCQ questionnaire containing 21 responses that represent the original questionnaire done on a sample 107 young adult participants.[16] The average age in that study was 19.9 years SD + 1.3 with range of 18-24 and 59% were males and 41% were female (n = 44); regarding education was 33 % did attended a college or a vocational school, 36 % were graduate from high school and 31 % of respondents quitted from school as compared to my study mean age of responded was 20.5922 SD + 1.854 with minimum age of 18 years and maximum age of 24 years. (Table no: 1). 90.2 % were male and 9.8% were female. (Graph no: 1). Mean duration of smoking was 3 years SD + 1.99 years with minimum duration was 6 months and maximum duration was 10 years. 79.2% were smoking for less than 5 years and 20.8% were smoking for 5-10 years.

Cronbach's alpha for the Negative consequence (NC) subscale in Myers16 was .79 (acceptable), although it was quite less as compared to full Negative consequence (NC) subscale. For the Negative reinforcement (NR) subscale Cronbach's was high (.95) (Excellent). For Positive reinforcement (PR) the Cronbach's alpha for the subscale was .94 (Excellent) and similar to the full Positive reinforcement (PR) subscale where it was .95(Excellent) and for Appetite and weight control (AWC) factor, total correlations for all items and the Cronbach's alpha for the subscale was .93 (Excellent). The overall Cronbach's alpha for the S-SCQ 21 items scale was .93 (Excellent).

My study had similar findings on a Pakistani young adult university student sample. The internal consistency was measured for all the four factors with Crohbach's Alpha for Positive reinforcement scale (PR) was .815 Appetite and weight control (AWC) was .837 (0.9 > α ≥ 0.8=Good) and for Negative reinforcement scale (NR) was .911, Negative consequences scale (NC) was .944 and for (α ≥ 0.9 =

Excellent) and Reliability Statistics for these four factors SSQ Crohbach's Alpha of .887 ($0.9 > \alpha \geq 0.8$=Good) and Crohbach's Alpha Based on Standardized Items .891 with an item means 26.707 and minimum score of 23.071 and 35.843 and a variance of 37.457. Scale statistics had a score of 106.83 with variance of 264.356 SD + 47.585.

The findings in my study is primarily an attempt to reinforce the extrapolative consistency of this instrument among Pakistani young adults and similar to the original study done Brandon and Baker SCQ for validation[13]. As in my study majority were current smokers(85.49 %) and I examined the scores for each four factors in relation smoking behavior as a continuous variable, whereas the other studies done on validation of SCQ sample included less than 65 % smoking currently and compared their scores across categories for smoking status or there might be another explanation for this inconsistency that it reflects a comparatively limited range for negative consequence (NC) scale in the group reflecting that the smokers had more anticipations for negative consequences irrespective of their recent smoking status.

Previous researches indicate that beliefs regarding weight control are considerably related to behavior of an adolescent regarding smoking.[17-19] These researches validate the adding up of controlling weight as a significant aspect in outcome expectancies for smoking, moreover this area need additional exploration to assess the usefulness of the weight control factor among adolescents.[20] My study have shown that the high item total correlation after correction and the correlational matrix for Appetite/ Weight Control Scale (AWC) of .846 and .509 respectively suggesting that the factor structure of this instrument is consistent within among Pakistani adolescent smoker. Also the positive expectancy scores in my for positive Reinforcement Scale items (PR) of .911 can be inferred as reliable with the researches given that there is increased smoking among young adult population. As such my study provides a preliminary substantiation for the relevance of this instrument especially among university students.

Further psychometric studies on smoking and use of other substance with larger and more representative samples for gender in adolescent and young adults is needed to determine a psychometric characteristics for use of this S-SCQ and also analysis for the short version of smoking consequence questionnaire (S-SCQ) for test and retest reliability should be done in a Pakistani population. It is also noteworthy that there is overestimation of these four factor correlations because this smoking consequence questionnaire (S-SCQ) was given to young adults in a university setting with a relative conservative environment especially for female youth. On the basis of these findings in my study a Pakistani version of short smoking consequences questionnaire should be evaluated for its psychometric properties. Finally, we also need to evaluate this S-SCQ among different cultural setting keeping in view or our diverse culture in different provinces whether these smoking outcome expectancies can be evaluated using this short version of smoking consequence questionnaire. My study offers a preliminary evidence for the use of this short version of smoking consequence questionnaire (S-SCQ) for smoking related outcome expectancies among Pakistani university young adults university students.

Limitation of Study

The findings of this study are limited to university students who are ex-smokers or smokers. The study was done in on university students about smoking consequences and outcome expectancies largely among current smokers and few ex-smokers; and sample was limited to one university and the data was cross-sectional so conclusions regarding cause and effect cannot be drawn. In this study I have only evaluated internal consistency and CFA to analyze reliability and factor analysis of instrument. Repeated measures for test-retest reliability were not included and model fitting analysis was not performed to improve the model fit.

CONCLUSION

The study concluded that S-SCQ had good to

excellent internal consistency and reliability. S-SCQ is valid instrument that can be used to evaluate smoking outcome expectancies among Pakistani adolescent and young population. This study can serve as an initial confirmation for use of short smoking consequence questionnaire (S-SCQ), among young adults and adolescent's Pakistani university and collegiate students that can evaluate outcome expectancies related to cigarette smoking.

It is recommended that a larger scale study should be conducted among different universities in public and private sector and also considering rural, urban and cultural background to assess smoking outcome expectancies that will not only provide a guideline for assessment of smoking behaviors but also help us to delineate guidelines for relapse prevention and instituting control strategies.

REFERENCES

1. World Health Organization. Global Tobacco Epidemic. Country Profiles Germany. 2015. Retrieved from: http: www. who. Int / tobacco / global_data / country _ profiles/en/. Last accessed, 10th Feburary, 2017.
2. Kirchner TR, Sayette MA. Effects of smoking abstinence and alchol consumption on smoking-related outcome expectancies in heavy smokers and tobacco chippers. Nicotine & Tobacco Research. 2007; 9:365–376.
3. Demographic and Health Survey Pakistan. 2014. Available at: http://www.nips.org.pk/abstract_files/PDHS%20Final%20Report%20as%20of%20Jan%2022-2014.pdf Retrieved 10th February 2010.
4. Leventhal AM, Schmitz JM. The role of drug use outcome expectancies in substance abuse risk: An interactional-transformational model. Addict Behav 206; 31: 2038–2062.
5. Hendershot CS, Witkiewitz K, George WH, Marlatt GA. Relapse prevention for addictive behaviors. Substance Abuse Treatment, Prevention, and Policy. 2011;6:17.
6. Marlatt GA. Cognitive factors in the relapse process. In: Marlatt, GA.; Gordon, JR., editors. Relapse prevention. Guilford Press; New York: USA. 1985; p. 128-200.
7. Abrams DB, Niaura RS.. Social learning theory. In: Blane, HT.; Leonard, KE., editors. Psychological theories of drinking and alcoholism. Guilford Press; New York: 1987; p. 181-226.
8. Donovan DM. Assessment of addictive behaviors: Implications of an emerging biopsychosocial model. In: Donovan, DM.; Marlatt, GA., editors. Assessment of addictive behaviors. Guilford Press; New York: 1998; p. 3-48.
9. Brown SA. Expectancies versus background in the prediction of college drinking patterns. Journal of Consulting and Clinical Psychology 1985; 53: 123–130
10. Stacy AW, Galaif ER., Sussman S, Dent CW, Myers MG, Brown SA. Self-generated drug outcomes in high-risk adolescents. Psychology of Addictive Behaviors 1996; 10, 18–27.
11. Schleicher H, Harris K, Catley D, Harrar S, Golbeck AL. An Examination of a brief Smoking Consequences Questionnaire for college students. Nicotine & tobacco research 2008; 10 (9): 1503-1509.
12. Rash CJ, Copeland AL. The Brief Smoking Consequences Questionnaire--Adult (BSCQ-A): development of a short form of the SCQ-A. Nicotine Tob. Res 2008; 10(11): 1633–1643.
13. Brandon TH, Baker TB. The Smoking Consequences Questionnaire: The subjective expected utility of smoking in college students. Psychological Assessment: A Journal of Consulting and Clinical Psychology 1991; 3: 484–491.
14. Wetter DW, Fiore MC, Young TB, McClure JB, de Moor CA, Baker TB. Gender differences in response to nicotine replacement therapy: Objective and subjective indexes of tobacco withdrawal. Experimental and Clinical Psychopharmacology 1999; 7: 135 – 144.
15. Copeland AL, Brandon TH. Do desirability ratings moderate the validity of probability ratings on the Smoking Consequences Questionnaire? Psychological Assessment 2002; 14: 353–359.
16. Meyer C, Rumpf HJ, Hapke U, John U. Prevalence of DSM-IV psychiatric disorders including nicotine dependence in the general population: results from the northern German TACOS study. Neurology, Psychiatry and Brain Research 2001; 9: 75–80
17. Hine DW, McKenzie-Richer A, Lewko J, Tilleczek K, Perreault L. A comparison of the meditational properties of four adolescent smoking expectancy measures. Psychology of Addictive Behaviors 2002; 16, 187–195.
18. Mettews G, Deary IJ, Whiteman MC. Personality traits. 2nd Edition. Cambridge University Press. 2003; p.1-33.
19. Kenford, SL, Smith SS, Wetter DW, Jorenby DE , Fiore,MC, Baker TB. Predicting relapse back to smoking: Contrasting affective and physical models of dependence . Journal of Consulting and Clinical Psychology 2002; 70:, 216 – 227
20. Jeffries SK, Catley D, Okuyemi KS, Nazir N, McCarter KS, Grobe JE et al.. Use of a Brief Smoking Consequences Questionnaire for Adults (SCQ-A) in African American Smokers. Psychology of Addictive Behaviors 2004; 18(1): 74–77.

EFFECTS OF SUGAR CANE JUICE (SACCHARUM OFFICINARUM L.) ON ARSENIC INDUCED HEPATOTOXICITY IN ALBINO RATS

Maria Nouman,[1] Raafea Tafweez,[2] Mah Jabeen Muneera[3]

How to cite: Nouman M, Tafweez R, Muneera MJ. Effects of sugarcane juice (Saccharium officinarum l.) on arsenic induced hepatotoxicity in albino rats. JAIMC. 2021; 19(1): 235-241.

Abstract

Background: Alarmingly high levels of Arsenic in drinking water have become a considerable risk for the whole world including Pakistan. Its chronic ingestion is leading to multi organ dysfunction. Sugar cane juice is extremely popular in Pakistan and contains anti-oxidant potential.

Objectives: To evaluate the effects of sugar cane juice against Arsenic induced hepatotoxicity in albino rats.

Methodology: This was an experimental animal study of four weeks. 36 male albino rats were divided into four groups. Group 1 was control group and received distilled water 1 ml/100g/day while group 2 was given sodium arsenite 0.5mg/100g/day dissolved in distilled water. Group 3 animals were given sugar cane juice 0.75 ml/100g/day and group 4 was given sodium arsenite 0.5 mg/100g/day and sugar cane juice 0.75 ml/100g/day. Dissection was performed at 29th day. Gross, histological and biochemical parameters were analyzed.

Results: Hepatotoxicity by Arsenic was confirmed in group 2 animals by elevated liver enzymes and histological picture of inflammation, pyknosis, vacuolization, congestion and fibrosis. Group 4 animals showed significantly lower values of serum liver enzymes. Histological improvement was seen in the form of preservation of hepatic structure and statistically significant reduction in inflammation and fibrosis. PAS staining showed glycogen accumulation and regeneration was seen in this group in the form of binucleation.

Conclusion: Sugar cane juice at a dose of 7.5 ml/kg is not only hepatoprotective against Arsenic but can also offer regeneration to the injured hepatocytes.

Key words: Arsenic, Sugar cane juice, Hepatotoxicity

Arsenic (Sankhiya) contamination in ground water has become a worldwide dilemma. It is a considerable health risk factor for many countries including Pakistan. WHO has established a maximum limit of 50 micrograms/ liter in drinking water[1]. Swiss Federal Institute has reported alarmingly dangerous levels of 200 micrograms/ liter along the Indus River Valley, the major source of water to Pakistan. This puts 50 to 60 million people at stake as they are using water that contains more than 50 micrograms/ liter of Arsenic, the values being 4 times the WHO's safety limit[1].

Arsenic exists in nature as pentavalent arsenate and trivalent arsenite, with arsenite being more toxic[2]. Once ingested it accumulates in vital organs and tissues leading to hepatotoxicity[2], nephrotoxicity[2], atherosclerosis, ischemic heart disease, hypertension and cancer of skin, lungs and bladder[3]. Arsenic is even reported in herbal medicines called Kushtas used by Pakistani Hakeems, the utilization of which is a major cause of renal failure[4].

Arsenic is rapidly absorbed from gastrointestinal tract and is carried to the liver for metabolism. Here arsenic is methylated and these methylated products are even more harmful than inorganic

1. Maria Nouman 2. Raafea Tafweez
3. Mah Jabeen Muneera
1. *Department of Anatomy, King Edward Medical University Lahore*
2. *Anatomy and Histology Department, King Edward Medical University, Lahore*
3. *Anatomy and Histology Department, Allama Iqbal Medical College, Lahore*

Correspondence:
Dr Maria Nouman, *Department of Anatomy, King Edward Medical University Lahore, Email: marriahnouman@gmail.com*

Submission Date: 12-10-2020
1st Revision Date: 16-11-2020
2nd Revision Date: 19-11-2020
Acceptance Date: 24-11-220

arsenic. Deposition of Arsenic has been confirmed in many vital organs but among these liver is the most frequently and commonly effected.[5] Arsenic hepatotoxicity leads to hepatocellular damage, inflammation, steatosis, necrosis, fibrosis resulting in liver carcinogenesis.[6] The hepatotoxicity also manifests itself by increase in liver enzymes (ALT, AST, ALP and bilirubin).

Arsenic hepatotoxicity is attributed to oxidative stress produced by the methylated products of Arsenic. The production of this stress is two folds; one is by the generation of reactive oxygen species (ROS) such as O_2^-, H_2O_2, OH and $^1O_2$. Second is by the suppression of anti-oxidant enzyme activity.[7]

Sugar cane (Saccharum Officinarum L.) is a large, strong growing species of grass. It is extensively grown in Asia[8] and is the second largest cash crop of Pakistan. It is not only grown for the production of sugar but its juice is hugely popular among the Pakistani populace. Sugar cane juice is widely used in the treatment of jaundice, hemorrhage, anuria, dysuria and other urinary symptoms.[9] In addition to its use as antiseptic and bactericidal it also has cardio tonic, diuretic and laxative effects. Various studies have demonstrated its anti-oxidant, anti-cance-rous and anti-inflammatory effects.[10] Modern pharmacological studies have indicated that sugar cane juice has hepatoprotective effect also.[8]

Sugar cane juice contains various fatty acids, phytosterols, terpenoids, flavonoids and phenols.[9] Presence of these flavonoids and phenols give sugar cane its antioxidant properties. Therefore, the present study was designed to evaluate the effect of sugar cane juice containing anti-oxidant properties against Arsenic induced oxidative stress.

METHODOLOGY

This experimental study of 28 days11 was conducted at Research Lab of Post graduate Medical Institute (PGMI), Lahore. Sample size of 36 rats was estimated by using 5% level of significance, 90% power of test with expected mean value of ALT (U/L) in group 1 as 26.20±7.07 and in group 4 as 83.00±6.86.[12]

36 male rats[12], weighing 100-150 g[13] were kept in the animal house under controlled conditions; temperature (27-30ºC), humidity (50±5%) and 12 hours of light and dark cycle. These were given commercially prepared food and water ad libitum and were acclimatized for 1 week.

The animals were randomly divided into four groups containing 9 animals each. Weight of the animals was recorded at the start and at the end of experiment and also recorded weekly to adjust the dose. The doses were given by oral gavage method. Group 1 served as a control group and was given only distilled water 1ml/100g/day[11]. Group 2 was the arsenic group and received sodium arsenite 0.5mg/100gm/day[11]. Group 3 was given sugar cane juice at a dose of 0.75ml/100g/day[12] and group 4 was given both sodium arsenite (0.5mg/100g/day) and sugar cane juice (0.75ml/100g/day).

500 mg of Sodium arse-nite (Sigma Chemicals) powder was dissolved in 1000 ml of distilled water to prepare a stock solution of sodium arsenite. This stock solution preparation and the Cane juice preparation and quantification were done by PCSIR Laboratories Lahore. Sugar cane was purchased from the local market. The stems were cut into uniform lengths of 0.4m and were then washed to remove any contaminants. Juice was extracted by using three-roller power crusher. It was then poured into a sterilized container after filtering with a muslin cloth, where it was pasteurized at 85-90 ºC for five minutes. pH of the pasteurized juice was adjusted at ≤ 4. After removing all the waxy material from the juice it was hot filled in sterilized bottles with air tight caps. Neither food preservative nor any ice was added at any stage of processing and standardizing. Bottles were then stored in the refrigerator at 4ºC.[12]

At the 29th day the animals were subjected to sacrifice one by one. They were trans-ferred to bell jar containing chloroform soaked cotton swab. After they were completely anaesthe-tized cardiac puncture was performed and the blood was collected

in the sterile vacutainers containing gel for biochemical assays. These vacutainers were placed in centrifuge machine operating at a speed of 3000 revolutions per minute for 10 minutes, which separated the serum from blood clot. A micropipette was used to transfer this clear serum into sterilized eppendorf tube which was then stored at -20ºC until these samples were used for liver enzymes assessment[12]. Estimation of ALT, AST, ALP and bilirubin was then performed by using kits of Human Company, Germany.

After the blood sampling, using all the aseptic measures dissection was performed. Liver was taken out and was observed grossly for its weight, color, surface and hemorrhagic spots. It was then cut into small pieces and was preserved in 10% formalin. Further processing of the liver tissue was done for its micro-scopic examination and was then visualized under microscope using H & E and PAS stain for infla-mmation, pyknosis, vacuolization, congestion and fibrosis. Micrometry was also performed to measure the size of hepatocytes.

Statistical Package for Social Sciences (SPSS) version 24 was used to analyze the results of the study. Quantitative variables were expressed as mean ± S.E (Standard error of mean). The qualitative variables were expressed as frequen-cies and percentages. Quantitative variables were compared by applying one way ANOVA. Difference between the groups was analyzed by using Post Hoc Tukey test. Chi square test was applied to observe the association between qualitative variables. p-value ≤ 0.05 was taken as statistically significant.

RESULTS

Taking control values as a reference,[14] there was weight gain in all the experimental animals but in group 2 the weight gain was significantly less as compared to the other groups. Moreover weight gain among group 1, 3 and 4 was not significantly different as depicted in table 1.

Mean values of liver weight from all four groups showed significant difference from each other and so was the case with RTWI. Upon applying Post hoc Tukey it was revealed that liver weight of group 2 and 4 was significantly different while there wasn't any difference in RTWI among the two groups.

The reference ranges of ALT, AST and ALP were taken as 10 to 40 U/L, 50 to 150 U/L and 30 to 130 U/L respectively15. Liver enzymes showed significant decrease in group 4 due to co-adminis-

Table 1: *Comparison of Groups in Body Weight and Liver Weight*

Parameters	Group-1 M±SE	Group-2 M±SE	Group-3 M±SE	Group-4 M±SE	P-value
Initial body weight(g)	106.78±5.97	113.11±10.35	112.00±10.42	110.56±6.56	0.436
Final body weight (g)	160.11±7.51	142.56±14.20	166.67±10.36	166.22±7.29	<.001
Liver weight (g)	6.51±0.52	5.07±0.54	6.71±0.58	6.19±0.31	<.001
RTWI	4.06±0.25	3.55±0.13	4.03±0.27	3.73±0.17	<.001

Note. One-way ANOVA, *p value ⩽ 0.05 is considered statistically significant
RTWI: Relative Tissue Weight Index

Table 2: *Comparison of Groups in Body Weight and Liver Weight*

Parameter	Group-1 M±SE	Group-2 M±SE	Group-3 M±SE	Group-4 M±SE	P-value
Serum ALT(U/L)	23.83±3.60	151.89±23.63	23.83±3.60	71.04±6.78	<.001
Serum AST(U/L)	59.26±7.02	176.17±6.54	69.11±10.58	115.68±14.37	<.001
Serum ALP(U/L)	90.52±17.10	174.74±26.12	100.65±20.28	135.01±7.15	<.001
Serum Total Bilirubin (mg/dl)	0.41±0.10	0.74±0.06	0.54±0.10	0.40±0.07	<.001

*p value ⩽ 0.05 is considered statistically significant

tration of sugar cane juice with arsenic as compared to group 2 in which the levels were raised to many times the control group. (Table 2)

The slides from group 1 showed normal architecture of liver. The portal triads containing a branch of hepatic artery, portal vein and bile duct was seen at the periphery. Polyhedral hepatocytes were present with one or two prominent nucleoli (Fig.2A). While in group 2 (Arsenic group), liver tissue lacked the picture of classical hepatic lobule. The radiating pattern was interrupted and the shape of hepatocytes was distorted, appearing to be shrunken (Fig.1). Vacuolization (100%) and pyknosis (77.7%) was evident (Fig.2B). Multiple foci of inflammatory cells were seen in 8 out of 9 animals. Widespread areas of congestion (88.9%) were present and even fibrosis (55.6%) was evident (Fig 2C). This fibrosis was either restricted to portal triads or in some areas it was bridging between the two triads. Staining these slides with PAS stain showed empty hepatocytes with no evidence of glycogen accumulation (Fig. 3B). Liver tissue from group 3 showed normal architecture. At some places cytoplasm showed focal vacuoles (44.4%) but upon staining with PAS stain these vacuoles turned out to be glycogen accumulation (Fig 3C). Group 4 which was given sugar cane juice with Arsenic showed much preservation in liver architecture (Fig 2E). There was significant decrease in the percentage of inflammation (33.3%), pyknosis (22.2%), vacuolization (22.2%), congestion (66.7%) and fibrosis (22.2%) as compared to group 2.

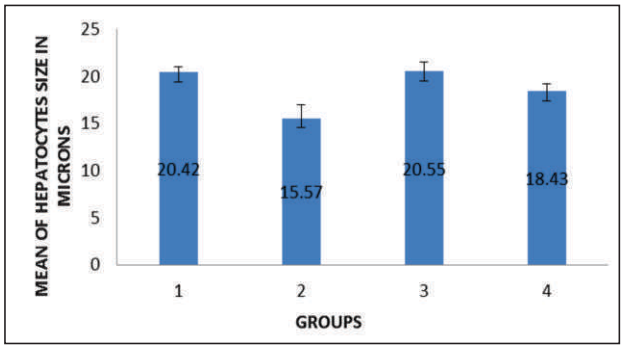


Fig.1: *Graph Showing Mean Values of Hepatocyte Size of Four Groups*

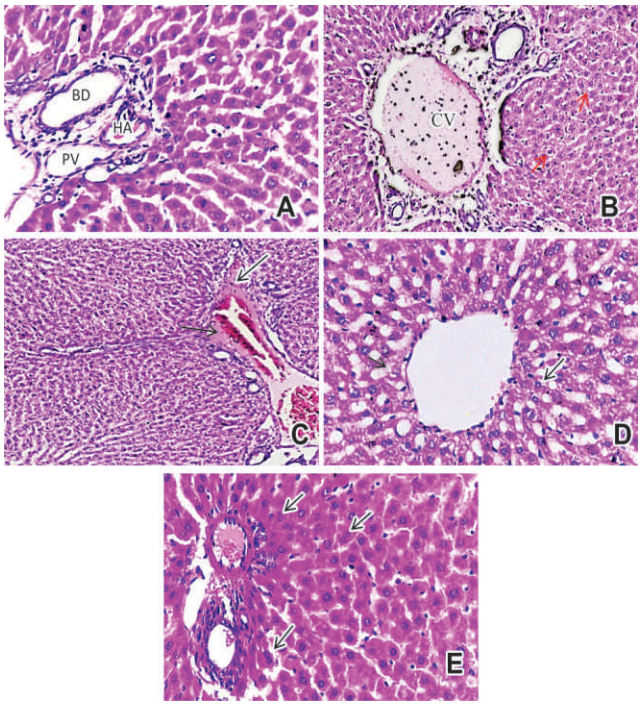


Fig.2: *Showing H & E. X400 slides from all four groups. A (group 1) is depicting normal polyhedral hepatocytes with portal triad containing hepatic artery HA, bile duct BD and portal vein PV. B & C X200 are slides from group 2, where B is showing distorted hepatic lobule and congestion with inflammatory cells in the central vein CV, red arrows are showing vacuolization, C is giving the picture of fibrosis (arrows). D (group 3) is showing cytoplasmic vacuolization (arrows) which in PAS stain appeared to be glycogen accumulation. E (group 4) showing polyhedral hepatocytes with binucleation (arrows) in some areas.*

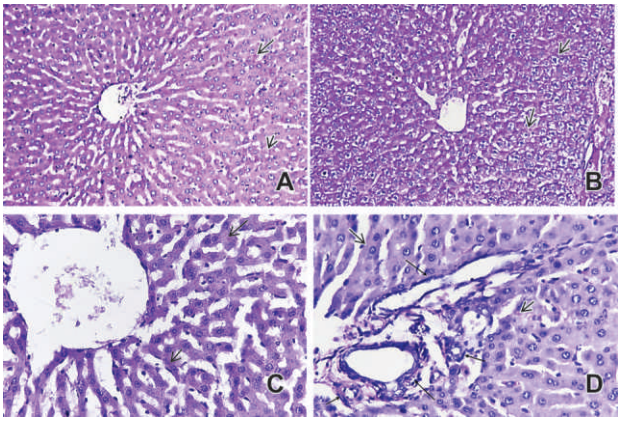


Fig. 3: *PAS stained slides from all four groups. A X200(group 1) is showing glycogen granules*

(arrows) within the cytoplasm. B X200 (group 2) is showing cytoplasmic vacuolization(arrows) C X400 (group 3) is depicting glycogen accumulation (arrows) in multiple areas with polyhedral hepatocytes. D X400 (group 4) preservation of liver architecture with glycogen accumulation (red arrows) is seen; arrows from above downwards show portal vein, hepatic artery and bile duct.

DISCUSSION

Arsenic, a known hepatotoxic agent, damages not only liver but other organs as well. Its pathogenesis is attributed to ROS (Reactive Oxygen Species). Contamination of Arsenic in drinking water has become a serious hazard. Many herbs and plants containing anti-oxidant properties have been tried against Arsenic toxicity but effectiveness of sugar cane juice against Arsenic had not been assessed yet. Therefore current study was planned to document efficacy of sugar cane juice against arsenic hepatotoxicity.

To assess the general health of animals, their weight was recorded. Animals from all the groups showed gain in body weight but group 2 (Arsenic group) showed significantly less weight gain than the other three groups. The mean values of weight gain in group 4 (166.22±7.29) showed no statistical difference from values of control group (160.11± 7.51) depicting their general status of well-being. This finding is concordant with Adil M et al (2015)[11] who have documented similar findings in their work on Arsenic toxicity. Similarly, mean liver weight of group 2 was also significantly decreased as compared to the other three groups. But in group 4 administration of sugar cane juice prevented this decrease, as also seen by Singh M et al (2018) in their review for hepatoprotective effect of herbalism against ethanol induced hepatotoxicity[16].

In the present study RTWI of group 2 animals showed a significant decrease than control group and even in group 4 this pattern continued. This finding is contrary to the work done by Adil M et al (2015) who has documented a rise in the mean value of RTWI in the Arsenic treated group[11]. This contradiction might be due to the reason that the weight of liver varies in different stages of liver injury. Inflammation, congestion and fatty change can lead to weight gain whereas fibrosis and necrosis might lead to decrease in weight. So a change in weight is an indicator for anything different going on from the control group at histological level.

To further augment the results, liver biomarkers ALT, AST, ALP and bilirubin levels were performed. The results showed elevated levels of these enzymes in group 2. Similar rise in these enzymes with arsenic was reported by Mohammadian M et al (2018),[17] Shafik NM et al (2016)[18] and Binu P et al (2018).[19] Liver enzymes are a marker of hepatocyte function and integrity. Membrane damage leads to the leakage of these enzymes from the hepatocytes. Chandrakar V (2018) showed that by generating ROS, Arsenic causes lipid peroxidation of the hepatocyte membranes and hence levels of liver enzymes elevate in serum[20]. The sugar cane plus Arsenic group (group 4) also depicted elevated levels of these enzymes as compared to control group. But the rise in enzyme levels in this group was significantly lower than the Arsenic treated group. This finding is supported by the study of Jiménez-Arellanes et al (2016); they reported the same results with cane juice[21]. A comment on the mechanism by which protection is afforded by sugar cane juice cannot be made as it was not in the scope of present study. Ji J et al (2019) showed that sugar cane juice possesses anti-oxidant activity due to its phenolic and flavonoids components. These anti-oxidants prevent the lipid peroxidation of membranes, maintaining the integrity of membranes.[22]

During histomorphometric analysis when micrometry was performed, shrinkage of hepatocytes was noted in group 2. This finding is also reported by Adil M.et al (2015)[11]. But this finding is contradictory to Uhunmwangho ES et al (2018),[23] who showed increase in the size of hepatocyte while working with a root extract against Arsenic. But this conflict might be because of the reason that their study duration was

only of nine days. In group 4, hepatocyte size was small as compared to control group but was significantly greater than group 2, showing the protection offered by cane juice.

The histological picture in group 2 showed destruction of liver tissue due to Arsenic. Inflammatory cells were not only present in periportal areas but even infiltrated the parenchyma. Cytoplasmic changes were seen in the form of vacuolization and nuclear changes depicted as pyknosis. Congestion was seen in the form of engorgement of veins. In our study we even witnessed the fibrosis of liver tissue due to Arsenic. In group 4 the histological picture was over all better than group 2. The percentage of all these changes got significantly reduced with administration of cane juice along with Arsenic. Our findings of hepatic protection with sugar cane juice are consistent with Khan SW et al (2015)[12] and Jiménez-Arellanes et al (2016)[21] who proved sugar cane juice as a hepatoprotective agent while studying against anti-tubercular drugs.

When tissues were stained with PAS stain, an interesting finding came out. The areas visible as vacuoles or spaces within the hepatocytes were PAS positive in animals of group 3 (sugar cane juice) and in some tissue preparations of group 4, confirming that these vacuoles were representing the glycogen stored within the hepatocyte whereas in group 2 (arsenic) similar type of vacuoles turned out to be PAS negative, therefore these spaces were most likely due to fat accumulation. Possibility of any other reason for this observation still remains, as specific stains for confirmation were not a part of study design.

CONCLUSION

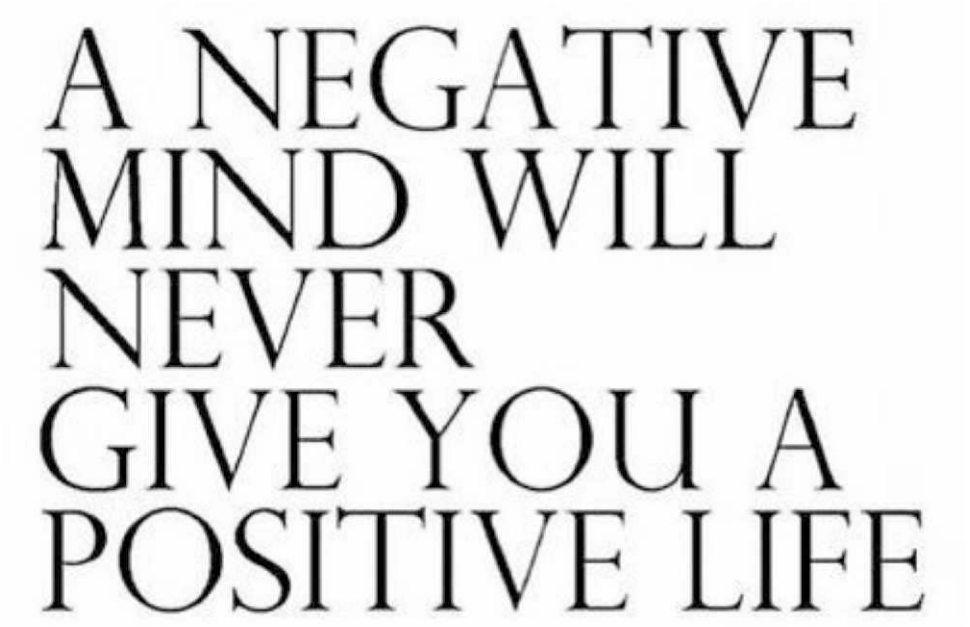
Arsenic proved to be hepatotoxic when given at a dose of 5 mg/kg and sugar cane juice proved to be hepatoprotective when administered at a dose of 7.5 ml/kg. The results of the study can offer cheap yet nutritious remedy against Arsenic toxicity.

REFERENCES

1. Guglielmi G. Arsenic in drinking water threatens up to 60 million in Pakistan. Science Aug. 2017;24: 2017.
2. Prakash C, Soni M, Kumar V. Mitochondrial oxidative stress and dysfunction in arsenic neurotoxicity: a review. Journal of Applied Toxicology. 2016 Feb;36(2):179-88.
3. Mendez WM, Eftim S, Cohen J, Warren I, Cowden J, Lee JS et al. Relationships between arsenic concentrations in drinking water and lung and bladder cancer incidence in US counties. Journal of Exposure Science and Environmental Epidemiology. 2017 May;27(3):235-243.
4. Shafique S, Naseem N, Javaid QU, Nagi AH. Histopathological Changes in Arsenic Kushta Induced Nephrotoxicity in Wistar Rats. JCPSP-Journal of the College of Physicians and Surgeons Pakistan. 2017 Feb 1;27(2):92-6.
5. Valko M, Jomova K, Rhodes CJ, Kuča K, Musílek K. Redox-and non-redox-metal-induced formation of free radicals and their role in human disease. Archives of toxicology. 2016 Jan 1;90(1):1-37.
6. Khairul I, Wang QQ, Jiang YH, Wang C, Naranmandura H. Metabolism, toxicity and anticancer activities of arsenic compounds. Oncotarget. 2017 Apr 4; 8(14):23905.
7. Shahid M, Niazi NK, Dumat C, Naidu R, Khalid S, Rahman MM et al. A meta-analysis of the distribution, sources and health risks of arsenic-contaminated groundwater in Pakistan. Environmental pollution. 2018 Nov 1;242:307-19.
8. Handayani ES, Nur A, Nugraha ZS, Ikhsani NW, Sakti FR, Akhmad SA. Ethanol Extract of Black Sugarcane Decrease Ischemia Volume and Bax Expression In Rats' Brain. International Journal of Human and Health Sciences (IJHHS). 2020 Jan 12; 4(2): 102-8.
9. Iqbal M, Qamar MA, Bokhari TH, Abbas M, Hussain F, Masood N et al. Total phenolic, chromium contents and antioxidant activity of raw and processed sugars. Information Processing in Agriculture. 2017 Mar 1;4(1):83-9.
10. Martelli G, Giacomini D. Antibacterial and antioxidant activities for natural and synthetic dual-active compounds. European journal of medicinal chemistry. 2018 Oct 5;158:91-105.
11. Adil M, Kandhare AD, Visnagri A, Bodhankar SL. Naringin ameliorates sodium arsenite-induced renal and hepatic toxicity in rats: decisive role of KIM-1, Caspase-3, TGF-β, and TNF-α. Renal failure. 2015 Sep 14;37(8):1396-40.
12. Khan SW, Tahir M, Lone KP, Munir B, Latif W. Protective effect of Saccharum officinarum L.(sugar

cane) juice on isoniazid induced hepatotoxicity in male albino mice. Journal of Ayub Medical College Abbottabad. 2015 Jun 20;27(2):346-50.

13. Gora RH, Baxla SL, Kerketta P, Patnaik S, Roy BK. Hepatoprotective activity of Tephrosia purpurea against arsenic induced toxicity in rats. Indian Journal of Pharmacology. 2014 Mar;46(2):197.
14. Dwivedi K. Study of effect of cadmium and arsenic toxicity on organs weight in relation to body weight. Indian Journal of Science Research and Technology, 3 (4). 2015:6-13.
15. Hasan KM, Tamanna N, Haque MA. Biochemical and histopathological profiling of Wistar rat treated with Brassica napus as a supplementary feed. Food science and human wellness. 2018 Mar 1;7(1):77-82.
16. Singh M, Hussain T, Firdous H, Shaikh S, Danish Rizvi SM, Moin et al. Preclinical hepatoprotective effect of herbalism against ethanol induced hepatotoxicity: a review. Current drug metabolism. 2018 Oct 1;19(12):1002-11.
17. Mohammadian M, Mianabadi M, Zargari M, Karimpour A, Khalafi M, Amiri FT. Effects of olive oil supplementation on sodium arsenate-induced hepatotoxicity in mice. International journal of preventive medicine. 2018;9.
18. Shafik NM, El Batsh MM. Protective effects of combined selenium and Punica granatum treatment on some inflammatory and oxidative stress markers in arsenic-induced hepatotoxicity in rats. Biological trace element research. 2016 Jan 1;169(1):121-8.
19. Binu P, Nellikunnath Priya MP, Abhilash S, Vineetha RC, Nair H. Protective effects of eugenol against hepatotoxicity induced by arsenic trioxide: An anti-leukemic drug. Iranian journal of medical sciences. 2018 May;43(3):305.
20. Chandrakar V, Dubey A, Keshavkant S. Modulation of arsenic-induced oxidative stress and protein metabolism by diphenyleneiodonium, 24-epibrassinolide and proline in Glycine max L. Acta Botanica Croatica. 2018 Apr 1;77(1):51-61.
21. Jiménez-Arellanes MA, Gutiérrez-Rebolledo GA, Meckes-Fischer M, León-Díaz R. Medical plant extracts and natural compounds with a hepatoprotective effect against damage caused by antitubercular drugs: A review. Asian Pacific journal of tropical medicine. 2016 Dec 1;9(12):1141-9.
22. Ji J, Yang X, Flavel M, Shields ZP, Kitchen B. Antioxidant and anti-diabetic functions of a polyphenol-rich sugarcane extract. Journal of the American College of Nutrition. 2019 Nov 17; 38(8): 670-80.
23. Uhunmwangho ES, Rasaq NO, Osikoya IO. Hepatoprotective effects of hexane root extract of Alchornea laxiflora in sodium arsenate toxicity in wistar albino rats. Chrismed Journal of Health and Research. 2018 Jan 1;5(1):38.



ASSOCIATION OF CONGENITAL HEART DISEASE WITH CONSANGUANITY

Allah Nawaz Sultan,[1] Nosheen Iftikhar,[2] Shabir Ahmed,[3] Ammara Kaleem,[4] Emran Roshan,[5] Mohammad Akram[6]

How to cite: Sultan AN, Iftikhar N, Ahmed S, Kaleem A, Roshan E, Akram M. Association of congenital heart disease with consanguinity. JAIMC. 2021; 19(1): 242-246.

Abstract

Objective: To determine the association of Consanguinity with Congenital Heart Diseases.

Methodology: This cases control study was done at department of Neonatology, The Children's Hospital and the Institute of Child Health, Lahore for six months. The Non-probability consecutive sampling technique was used to include patients. After taking informed consent from parents of neonates, their demographic information including name, age, sex, address, date of admission was recorded. History was taken and presence of consanguinity was labeled as per operational definition. Data analysis was done by SPSS version 17. Association of the disease with Consanguinity was determined. Odd ratio was calculated for the comparison and the significance level was $p<0.05$.

Results: In our study the mean age of the children was 13.15±7.12 days. In this study 46.36% children were males and 53.64% children were females. The consanguinity was found in 63(57.3%) in which 41 were from case group and 22 were from control group causing the OR=4.39. This showed that there are 4 times greater risk of CHD in children whose parents have consanguinity.

Conclusion: There is significantly more risk of congenital Heart diseases with consanguinity.

Keywords: Congenital Heart Disease, Consanguinity, Children

Consanguinity which is defined as the marriage of two persons with common ancestors, often has strong genetic association for offspring. Consanguinity exacerbates the primary genetic risk factors; especially in the offspring of first cousins.[1] Congenital Heart Disease (CHD) is the most frequently observed congenital anomaly in the newborns with an incidence of about 8 /1000 live births.[2] Male outnumbered Females with the ratio of 1.6:1.[2,3] Acyanotic lesions are more frequent than Cyanotic lesions. Ventricular Septal Defect (VSD) is the most common (31%) followed by Patent Ductus Arteriousus (16.3%)[4]. FallotsTetrology is the most frequent Cyanotic lesion (7.8%).[4] Consanguineous marriage have been linked with an increased risk of various forms of inherited diseases[5]. It was also determined that first level consanguinity was found in 66% of cases of Congenital Heart Disease[6]. Existing literature showed that there was significant comparison between controls and patients having Atrial Septal Defect (p=0.000) and Ventricular Septal Defect (p=0.000).[2] There was also found significant odd ratio for first cousin marriage OR= 4.76 with confidence interval (2.57-8.89).[2] The exact incidence and prevalence of Congenital Cardiac Disease is not known in our country.[7] Considering the increased consanguineous marriages in our country, the risk is certainly higher than other countries.[7]

The rationale of the study is to educate the masses about the association of Congenital Heart Diseases with consanguinity and to help them avoid cousin marriages, whenever possible.

1. Allah Nawaz Sultan
2. Nosheen Iftikhar
3. Shabir Ahmed
4. Ammara Kaleem
5. Emran Roshan
6. Mohammad Akram

1,2,5,6. Sharif Medical & Dental College, Lahore
3,4. Azra Naheed Medical College, Lahore

Correspondence:
Dr. Shabbir Ahmed, Associate Professor, Azra Naheed Medical College, Lahore

Submission Date: 10-10-2020
1st Revision Date: 21-11-2020
Acceptance Date: 29-11-2020

METHODOLOGY

A Case control study was conducted in the department of Neonatology, The Children's Hospital and the Institute of Child Health, Lahore after taking approval from the ethical committee. The study was done from 1st January 2018 to 30th June 2018. Sample size of 110 (55 in both groups) was calculated with 80% Power of test and significance level was 1% and taking expected percentage of consanguinity (as per operational definition) in both groups that is 66.2 % in with Congenital Heart Disease group Vs 35.6 % in without Congenital Heart Disease group. We included patients 1-28 days old of both sexes. We defined our patients as Cases in whom there was presence of congenital heart disease. These were detected by Echocardiography performed in the first 28 days of life. Controls were healthy neonates without Congenital Heart Disease. One hundred and ten patients (55 cases and 55 controls) who fulfilled the inclusion criteria were included in the study. After taking written consent from parents of neonates, their demographic information including name, age, sex, address, date of admission were recorded. History was taken and presence of consanguinity was identified as per operational definition.

Data was analyzed by software Statistical Package for the Social Sciences (SPSS) version 24. Association of The disease with Consanguinity was determined. Odd ratio was calculated for the comparison and the significance level was $p<0.05$.

RESULTS

In our study total 110 children were enrolled. The mean age was 13.15±7.12 days with minimum and maximum days of 2 & 27 days respectively. Table.1

In this study 46.36% children were males and 53.64% children were females. The female to male ratio of the children was 1.15:1. Fig.1

In our study the consanguinity was found in 63(57.3%) patients and it was not found in 47(42.7 %) patients. Table.2

In our study the consanguinity was noted in 63 children in which 41 were from case group and 22 were from control group, similarly the consanguinity was not found in 47 children in which 14 were from case group and 33 were from control group. Statistically there is 4 times greater risk of consanguinity was found in case group children as compared to control group children. i.e OR=4.39. Table.3

Table 1: Descriptive statistics of age (days)

Age (Days)	**N**	110
	Mean	13.15
	SD	7.12
	Minimum	2.00
	Maximum	27.00

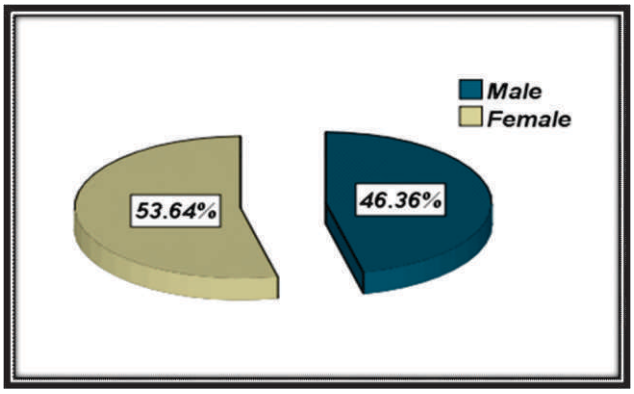


Fig # 1: *Frequency Distribution of Gender*

DISCUSSION

Previously many articles have been published which showed link between consanguineous marria-

Table 2: Frequency distribution of consanguinity

Consanguinity		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NO	47	42.7	42.7	42.7
	YES	63	57.3	57.3	100.0
	Total	110	100.0	100.0	

Table 3: Comparison of consanguinity in both study groups

		Study group		Total
		Case	Control	
Consanguinity	**Yes**	41	22	**63**
	No	14	33	**47**
Total		**55**	**55**	**110**

Odd Ratio = 4.39 [95% CI; 1.951, 9.983]

Table 4: Frequency of acyanotic heart diseases

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Acyanotic Heart Disease (ACHD)	23	20.9	20.9	20.9
	Ventricular Septal Defect (VSD)	19	17.3	17.3	38.2
	Atrial Septal Defect (ASD)	7	6.4	6.4	44.5
	Atrioventricular Septal Defect (AVSD)	3	2.7	2.7	47.3
	Patent Ductus Arteriosus (PDA)	3	2.7	2.7	50.0
	No Congenital Heart Disease	55	50.0	50.0	100.0
	Total	110	100.0	100.0	

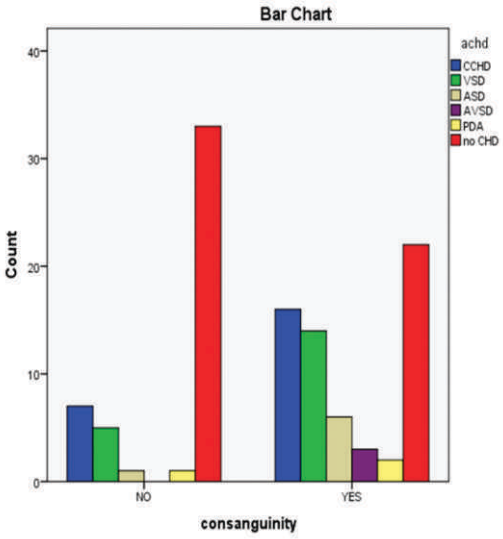
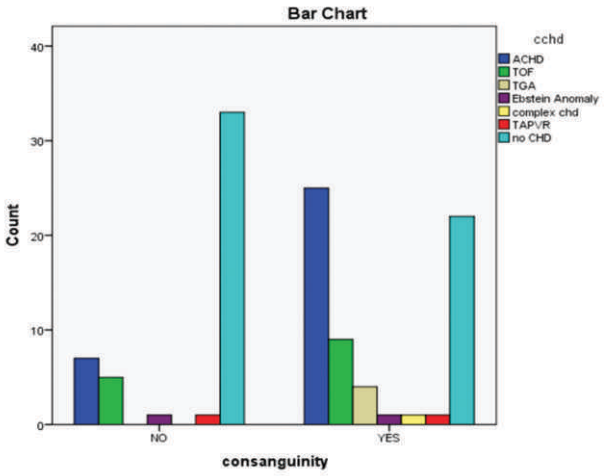


Table 5: Frequency of cyanotic congenital heart diseases

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Cyanotic Congenital Heart Diseases (CCHD)	32	29.1	29.1	29.1
	Tetrology of Fallots (TOF)	14	12.7	12.7	41.8
	Transposition of Great Arteries (TGA)	4	3.6	3.6	45.5
	Ebstein Anomaly	2	1.8	1.8	47.3
	complex Congenital Heart Defects	1	.9	.9	48.2
	Total Anamolous Pulmonary Venous Return (TAPVR)	2	1.8	1.8	50.0
	No Congenital Heart Disease	55	50.0	50.0	100.0
	Total	110	100.0	100.0	



ge and increased incidence of congenital heart disease. Ventricular septal defects and atrial septal defects were found to be the most commonly seen disorders. The demographic data are often not clear but in many studies the results suggest a link between consanguinity and congenital cardiac disease.[8] The consanguinity has strong association with many congenital malformations out of which congenital heart disease has been studied by several authors from high consanguinity rate countries.[9-11]

In our study the consanguinity with CHD was more common in females than to male children. According to our study in cases there is 4 times more risk of CHD disease than to control group. In this study the consanguinity was noted in 63 children in which 41 were from case group and 22 were from control group, similarly the consanguinity was not found in 47 children in which 14 were from case group and 33 were from control group. Highly significant difference was noted between the study groups and consanguinity. i.e p-value=0.000. Some of the studies are discussed here supporting the results of our study as.

A study by Zaid R, Al-ani[6] demonstrated in their study that the consanguinity is a proved risk factor for congenital heart diseases. In this study cases were 86, in 78% of cases consanguinity was found. Consanguinity was seen in 43.3% in controls. Consanguinity was identified to be a well-documented risk factor. It was also observed that consanguinity affects the VSD and ASD more than TOF subtypes.

In addition it was also observed that the parental age and gender of infants were not risk factors. In another article by Yuniset al.[12] analysis of subtypes of congenital cardiac diseases was done and VSD was found to be linked with first-cousin marriage.

Numerous other studies demonstrated that the incidence of congenital heart disease (CHD) is higher in families with higher consanguinity. In a population with a higher birth rate, consanguinity may increase the underlying genetic risk factors, especially in the children of first cousins. It shows that in the genetic transmission of some cardiac defects there may be a recessive component.[13,14] Existing literature showed that there was significant comparison between controls and patients having Atrial Septal Defect (ASD) (p=0.000) and Ventricular Septal Defect (VSD) (p=0.000).[2] There was also found significant odd ratio for first cousin marriage OR= 4.76 with confidence interval (2.57-8.89).[2]

Roodpeyma et al. [2002] carried out a study in which 346 cases of congenital heart disease (CHD) admitted to Taleghani Hospital, Tehran, Iran were enrolled. Same number of controls were also enrolled. The results of this study showed the presence of consanguinity in 22.0% of cases and in 19.1% of control. The results did not achieve statistical significance at P < 0.05.15In South India, a study was done by Ramegowda and Ramachandra [2006].[16] They studied 144 cases of congenital heart disease registered from three major hospitals. This study recommended evidence of transmission of CHDs via consanguinity.

Chehab et al. [2007][17] conducted a study in Lebanon. In this study 1,585 cases of nonsyndromic CHD were enrolled. 1,979 controls without CHD from the same area were also enrolled. The results showed that consanguinity was present more in CHD cases versus controls.

One more study by Nabulsiet al.[18] showed that in first cousin marriages there is a significantly higher proportion of individuals with different types of CHD including aortic valvular defects, atrial septaldefects , ventricular septal defects , tetralogy of Fallot (TOF), and pulmonic stenosis.

Mohd Ashraf et al,[19] demonstrated in their study that the CHD is more common and severe in those children who are born of consanguineous marriage, and CHD is more frequently seen in female children.

CONCLUSION

According to our study there is significantly more risk of congenital Heart diseases with consanguinity in cases than to controls groups. Our study also showed that the CHD due to consanguinity was more common in females than in male children. So our recommendation is to avoid cousin marriages whenever possible.

REFERENCES

1. Becker SM, Al Halees Z, Molina C, Paterson RM. Consanguinity and congenital heart disease in Saudi Arabia. Am J Med Genet 2001;99(1):8-13.
2. Nikyar B, Sedehi M, Mirfazeli A, Qorbani M, Golalipour M-J. Prevalence and pattern of congenital heart disease among neonates in Gorgan, Northern Iran (2007-2008). Iran J Pediatr 2011; 21(3): 307.
3. Farooqui R, Haroon UF, Niazi A, Rehan N, Butt TK, Niazi M. Congenital heart diseases in neonates. Journal of Rawalpindi Medical College (JRMC) 2010;14(1):31-2.
4. Ashraf M, Chowdhary J, Khajuria K, Reyaz A. Spectrum of congenital heart diseases in Kashmir, India. Indian Pediatr 2009;46(12):1107-8.
5. Shieh JT, Bittles AH, Hudgins L. Consanguinity and the risk of congenital heart disease. Am J Med Genet 2012;158(5):1236-41.
6. Al-Ani ZR. Association of consanguinity with congenital heart diseases in a teaching hospital in Western Iraq. Saudi medical journal 2010; 31(9): 1021-7.
7. Hassan M, Ahmed N, Mushtaq F, Iqbal S. Congenital heart disease in children admitted to Childrens Hospital at Pakistan Institute of Medical Sciences (PIMS). J Pak Inst Med Sci 1995;6:334-8.
8. Bittles AH. Assessing the influence of consanguinity on congenital heart disease. Ann Pediatr Cardiol 2011;4(2):111.
9. Wahab AA, Bener A, Teebi AS. The incidence

patterns of Down syndrome in Qatar. Clin Genet 2006;69(4):360-2.

10. Al-Gazali L, Dawodu A, Sabarinathan K, Varghese M. The profile of major congenital abnormalities in the United Arab Emirates (UAE) population. J Med Genet 1995;32(1):7-13.
11. Niazi M, Al-Mazyad A, Al-Husain M, Al-Mofada S, Al-Zamil F, Khashoggi T, et al. Down's syndrome in Saudi Arabia: incidence and cytogenetics. Hum Hered 1995;45(2):65-9.
12. Yunis K, Mumtaz G, Bitar F, Chamseddine F, Kassar M, Rashkidi J, et al. Consanguineous marriage and congenital heart defects: A case-control study in the neonatal period. Am J Med Genet Part A 140A 2006: 1524-30.
13. Nabulsi MM, Tamim H, Sabbagh M, Obeid MY, Yunis KA, Bitar FF. Parental consanguinity and congenital heart malformations in a developing country. Am J Med Genet 2003;116(4):342-7.
14. Tikkanen J. Risk factors for congenital heart disease. Health Services Research by the National Board of Health in Finland, Helsinki: the University of Helsinki; 1986.
15. Roodpeyma S, Kamali Z, Afshar F, Naraghi S. Risk factors in congenital heart disease. Clin Pediatr 2002;41(9):653-8.
16. Ramegowda S, Ramachandra NB. Parental consanguinity increases congenital heart diseases in South India. Ann Hum Biol 2006;33(5-6):519-28.
17. Chehab G, Chedid P, Saliba Z, Bouvagnet P. Congenital cardiac disease and inbreeding: specific defects escape higher risk due to parental consanguinity. Cardiol Young 2007;17(04):414-22.
18. Nabulsi AA, Folsom AR, White A, Patsch W, Heiss G, Wu KK, et al. Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. New England Journal of Medicine 1993;328(15):1069-75.
19. Ashraf M, Malla RA, Chowdhary J, Malla MI, Akhter M, Rahman A, et al. Consanguinity and pattern of congenital heart defects in Down's syndrome in Kashmir, India. Am J Sci Ind Res 2010; 1: 573-7.
20. McGregor TL, Misri A, Bartlett J, Orabona G, Friedman RD, Sexton D, et al. Consanguinity mapping of congenital heart disease in a South Indian population. PloS one 2010;5(4):e10286.

FETOMATERNAL OUTCOME IN PREGNANCY WITH CARDIAC DISEASE

Aymen Javed,[1] Robina Tariq,[2] Zahida Noreen,[3] Areeba[4]

How to cite: Javed A, Tariq R, Noreen Z, Areeba. Fetomaternal outcome in pregnancy with cardiac disease. JAIMC. 2021; 19(1): 247-250.

Abstract

Introduction: Incidence of cardiac diseases in pregnancy is increasing, partly due to better management of congenital heart diseases and partly due to early diagnosis of rheumatic heart disease. It is a great challenge for pregnant lady as well as for obstetrician. Cardiac disease in pregnant females may cause adverse outcomes both for mother as well as for baby.

Objective: To determine the fetomaternal outcome in pregnant females with cardiac disease.

Methodology: It is a descriptive cross-sectional study conducted between January 2020 to November 2020 in Services hospital Lahore. Non-probability purposive sampling technique was used. Data from patients fulfilling the inclusion criteria was recorded in preformed proforma. We noted the following variables for maternal outcome i.e. ICU admission, mortality and mode of delivery. For fetal outcome we measured prematurity, birth weight and perinatal mortality.

Results: A total of 48 women were enrolled in the study, out of which 32 (66%) of the patients were multigravida and 16 (34%) were primigravida. The mean age of the patients was 28.7 years± + 5. 001. Most common cardiac disease was Rheumatic Heart Disease, i.e., 38 (79%), while the second most common was congenital heart disease with a total of 4 (8%) patients. Out of 48 patients 16 required ICU admission, 11 were discharged after treatment and 5 patients expired in ICU. In fetal outcome, preterm babies were 25 (52%), while term babies were 23 (48%). A total of seven (14.6%) babies were of low birth weight and 41 (85.4%) were of normal birth weight.

Conclusion: Cardiac disease in pregnancy causes many fetomaternal complications so mass level campaigns are required to encourage supervised pregnancy.

Keywords: Cardiac disease in pregnancy, complication, fetomaternal outcome.

Pregnancy is a challenge to all body organs. Similarly, pregnancy with cardiac disease is a challenge to obstetricians as well as to the patient. Breathlessness, pedal oedema and cardiac murmur are features of normal pregnancy as well as in cardiac disease; so it may cause difficulty in clinical diagnosis.[1] Prevalence of heart disease in pregnancy vary from 0.3-3.5% in various study.[2]

Pregnancy is associated with an increase in cardiac output. This increase in cardiac output is usually between 30-50%. Labour causes a further increase in cardiac output, which may cause an extra burden on the already compromised heart.[3] Although there is a lot of improvement in obstetrical and neonatal management recently, there is still high fetal and maternal morbidity and mortality. The actual risk depends on the type and severity of the cardiac disease, but it may cause 33% maternal mortality.[4]

Pregnancy with cardiac disease may cause complications to both the mother and baby. The mother may suffer from pre-term labour, pre-eclampsia, an increase in ICU admission and death.[5] Similarly, the fetus may suffer from low birth weight, prematurity and perinatal mortality. Cardiac disease in pregnancy poses diagnostic and manage-

1. Aymen Javed
2. Robina Tariq
3. Zahida Noreen
4. Areeba

1-4. Department of Obstetrics and Gynaecology, Services Hospital Lahore.

Correspondence:
Dr. Aymen Javed, *Senior Registrar, Department of Obstetrics and Gynaecology, Services Hospital Lahore aymenasif86@gmail.com*

Submission Date: 24-12-2020
1st Revision Date: 29-12-2020
Acceptance Date: 31-12-2020

ment challenges.[6] The objective of the study to determine the fetomaternal outcome in preg-nant females with cardiac disease.

METHODOLOGY

It was a descriptive cross-sectional study conducted between January 2020 to November 2020. This study was conducted at the Services Hospital Lahore. A non-probability purposive sampling technique was used. All the pregnant females with cardiac disease diagnosed by echocardiography, ECG and enzyme assays were included in the study. All the patients having other co-morbidities like chronic renal failure, diabetes mellitus and chronic liver disease were excluded from the study. Patients fulfilling the inclusion and exclusion criteria were enrolled in the study after informed consent. After admission, patients were examined daily for cardiac status as well as for the fetal wellbeing.

All the information was recorded in a predesigned proforma.We noted the following variables for maternal outcome i.e. ICU admission, mortality and mode of delivery. For fetal outcome we measured prematurity, birth weight, intrauterine death and perinatal mortality.

Patients were assessed for the mode of delivery by the consultant obstetrician in liaison with the cardiologist. Patients were planned for a spontaneous vaginal delivery if not having any contraindications for it. Patients in whom there was any indication of caesarean section were scheduled for operative delivery. Medical management, as advised by cardiologist was continued accordingly.

RESULTS

A total of 48 women were enrolled in the study. The mean age of the patients was 28.7 years± 5.001. A total of 32 (66%) of the patients were multigravida and 16 (34%) were primigravida. Further distribution is explained in figure 1.

The most common cardiac disease was Rheumatic Heart Disease, i.e., 38 (79%), while the second most common was congenital heart disease with a total of 4 (8%) patients. Other diseases like Dilated Cardiomyopathy, Peripartum Cardiomyopathy and Ischemic Heart Disease were present in 3 (6%), 2(4.1%) and 1(2%) patients, respectively. Further distribution is explained in figure 2.

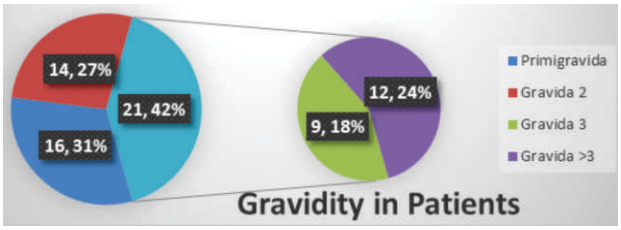
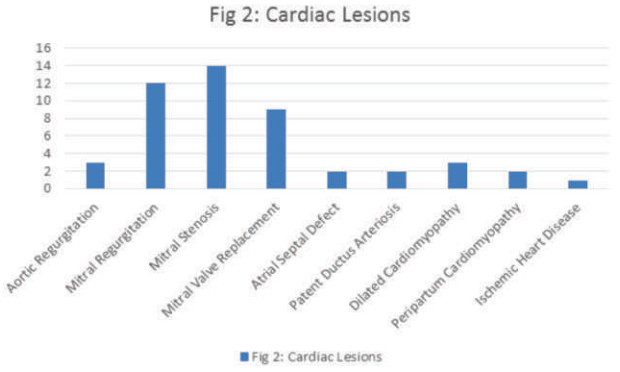


Fig. 1: *Gravdidity in Patients*

The ejection fraction was normal in majority of patients, i.e., 34 (70%), mild dysfunction (40-49% ejection fraction) was observed in 5(10.4%), moderate dysfunction (30-39%) was observed in 6 (12.5 %) and severe dysfunction was seen in 3 (6.2%) of the patients.



A total of 07 (14.5%) patients expired during the peripartum period. Majority of the patients were delivered by Lower Segment Caesarean Section, i.e., 32 (66.7%). Details of maternal outcome are given in Table 1.

Table 1: *Maternal Outcome in Pregnant Cardiac Patients*

	Maternal outcome	n (%)
Mode of delivery	Spontaneous Vaginal Delivery	16 (33.3%)
	Lower Segment Caesarean Section	32 (66.7%)
Mortality	Expired after ICU admission	5 (10.4%)
	Expired during surgery	2 (4.2%)
ICU Admission	Successfully discharged after treatment	11 (22.9%)
	Expired in ICU	5 (10.4%)

A total of 46 (96%) babies remained alive while two (4%) babies were expired. Preterm babies were 25 (52%), while term babies were 23 (48%). A total of seven (14.6%) were low birth weight and 41 (85.4%) were of normal birth weight. The mean birth weight of the children was 2.84 Kg ± 0.53. (Figure 3)

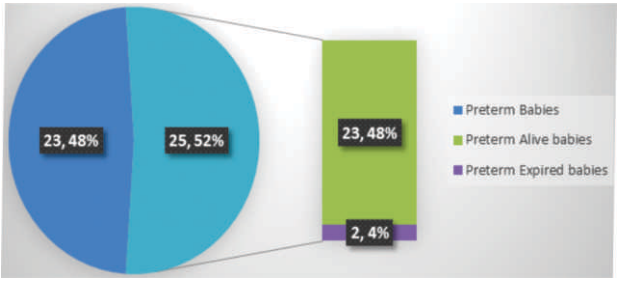


Figure 3: *Fetal Outcome in Cardiac Patients.*

Note:- Red area in the figure indicate percentage of term alive babies (48%).

DISCUSSION

Pregnancy is known to affect hemodynamic and cardiovascular functions. Pre-existing heart disease increases the risk of complications. Our study revealed that approximately 15% of women and 4% of babies were expired. This is different from other studies conducted by Gahlot K et al. and Pakdey K et al.; their study's mortality rate was 8% and 5.6%, respectively.[7,8] This number may be high due to unsupervised pregnancies as the prevalence of un-booked patients is about 42% in Pakistan.[9]

In our study, Rheumatic Heart Disease (RHD) was the most common cause of heart disease, followed by dilated cardiomyopathy, while only one patient had ischemic heart disease. RHD was also the leading cause reported by other studies of South Asia.(7,8) The higher incidence of RHD may be attributed to the inappropriate treatment of Streptococcal infection in childhood.

On the other hand incidence of Ischemic Heart Diseases is increasing in developed countries. Few recent studies have reported a figure of 4%, which is higher than our study results.[10] The rate of LSCS was higher in our study to be 67%, which is higher than studies.[7,9] The higher incidence of mortality may be attributed to the fact that there are many unsupervised un-booked pregnancies, which leads to delayed diagnosis and in appropriate management of potential risks at earlier stage.

A total of 52% of the babies were delivered preterm and 48% were term babies. The present study also showed a 10% mortality rate in neonates and 33% admission in ICU, comparable with other studies of this region.[7,9]

CONCLUSION

Pregnancy in cardiac patients can cause complications and lead to mortality, not only for mothers but also for babies. As in our cohort Rheumatic heart disease is the most common cardiac disease so training and awareness of General Physicians, Paediatricians and the public is required to prevent it. Similarly, mass level campaign for the need of supervised pregnancies is also a very relevant suggestion.

REFERENCES

1. Davies GAL, Herbert WNP. Assessment and Management of Cardiac Disease in Pregnancy. J Obstet Gynaecol Canada [Internet]. 2007 [cited 2020 Dec 28];29(4):331–6. Available from: https:// pubmed. ncbi. nlm.nih.gov/17475126/
2. Burlingame J, Horiuchi B, Ohana P, Onaka A, Sauvage LM. The contribution of heart disease to pregnancy-related mortality according to the pregnancy mortality surveillance system. J Perinatol [Internet]. 2012 Mar [cited 2020 Dec 28]; 32(3): 163–9. Available from: https:// pubmed. ncbi. nlm. nih. gov/21660084/
3. Ferrazzi E, Stampalija T, Monasta L, Di Martino D, Vonck S, Gyselaers W. Maternal hemodynamics: a method to classify hypertensive disorders of pregnancy. Am J Obstet Gynecol. 2018 Jan 1; 218(1): 124. e1- 124.e11.
4. Hameed A, Karaalp IS, Tummala PP, Wani OR, Canetti M, Akhter MW, et al. The effect of valvular heart disease on maternal and fetal outcome of pregnancy. J Am Coll Cardiol [Internet]. 2001 Mar 1 [cited 2020 Dec 28];37(3):893–9. Available from: https://pubmed.ncbi.nlm.nih.gov/11693767/
5. Roos-Hesselink J, Baris L, Johnson M, De Backer J, Otto C, Marelli A, et al. Pregnancy outcomes in women with cardiovascular disease: evolving trends over 10 years in the ESC Registry Of Pregnancy And Cardiac disease (ROPAC). Eur Heart J [Internet].

2019 Dec 14 [cited 2020 Dec 28];40(47):3848–55. Available from: https://academic.oup.com/eurheartj/ article/40/47/3848/5419276

6. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet [Internet]. 2006 Apr 1 [cited 2020 Dec 28];367(9516):1066–74. Available from: https://pubmed.ncbi.nlm.nih.gov/16581405/
7. Pandey K, Verma K, Gupta S, Jahan U, Kirti N, Gupta P. Study of pregnancy outcome in women with cardiac disease: a retrospective analysis. Int J Reprod Contraception, Obstet Gynecol. 2016;5(10): 3537–41.
8. Gahlot K, Singh P, Pandey K. Pregnancy outcome in women with heart disease at a tertiary referral teaching center in Northern India. Int J Reprod Contraception, Obstet Gynecol [Internet]. 2016 Feb 3 [cited 2020 Dec 28];5(9):3056–9. Available from: http://dx.doi.org/10.18203/2320-1770.ijrcog 20162984
9. Kalim D. FREQUENCY OF MATERNAL AND PERINATAL COMPLICATIONS AMONG BOOKED AND UN-BOOKED ANTENATAL WOMEN [Internet]. Vol. 7, KMUJ 2015. 2015 [cited 2020 Dec 28]. Available from: https:// www.kmuj.kmu.edu.pk/article/view/174
10. Kealey AJ. Coronary artery disease and myocardial infarction in pregnancy: A review of epidemiology, diagnosis, and medical and surgical management. Can J Cardiol [Internet]. 2010 [cited 2020 Dec 28]; 26(6):e185. Available from:/pmc/articles/ PMC 2903989/ ?report=abstract

IMPORTANCE OF IDENTIFYING CONFOUNDERS IN AN EXPERIMENTAL STUDY

Muhammad Faraz Khalid

How to cite: Khalid MF. Importance of identifying confounders in a experimental study. JAIMC. 2021; 19(1): 251-252.

Abstract

Confounding is one of the three major types of bias in a statistical work. In a statistical study, any factor that affects the effect of independent variable on a dependent variable such as final results do not depict the actual relationship between the variables is considered a confounder. It is also referred to as confounding variable/factor, lurking variable). This short commentary highlights the origin of confounders in healthcare services, how they are identified and dealt.

CONCEPT OF CONFOUNDING

Confounding is one of the three major types of bias in statistical work (the other two being selection bias and information bias). In statistical studies, any factor that affects the effect of independent variable on a dependent variable such that final results do not depict the actual relationship between the variables,[6] is considered a confounder (also referred to as confounding variable/factor, lurking variable),[1]. The same can be taken for epidemiological studies involving exposure (independent variable) and its outcome (dependent variable). The confounders depict such correlations which actually don't even exist. In other words we can say that confounder is a variable, in addition to the independent variable, that affects the dependent variable. Thus they can ruin an experimental study by changing the results, if one does not take into account that which confounding variables might be present and what effects they might have on the dependent and independent variables, before designing an experiment.[2]

FROM WHERE A CONFOUNDER CAN ARISE IN HEALTHCARE SERVICES?

Several factors, on various levels, can be a source of confounding in healthcare systems. Which intervention is to be used in a particular patient is determined by the various factors at level of the system, physician and the patient him/herself.[7] To give an example, the physician may base his decision of treatment upon the severity of the disease, his past experience about an intervention and its prognosis or on his assessment of the patient's inclination to cling to the prescribed therapeutic measure. Patient's factors may include their cultural and ethical beliefs regarding the disease, their trust on the physician and their monetary conditions. These factors blend in a unique and complex way to affect the outcome of a healthcare service as a whole. In most of the studies based on healthcare utilization database, such potential confounders are either not properly measured or are unclear, making the relationship between the exposure and the outcome shown by the study, less reliable.

HOW A CONFOUNDER CAN BE IDENTIFIED?

In a study, a confounder can be identified by the following general characters (Fig 1):

1) It is associated with the independent variable (exposure) being studied. In other words, it should be a factor that is not equally distributed among the subject groups and on the basis of which subjects can be differentiated from each other.[5]
2) In the absence of the independent variable a true confounder can predict the outcome

1. Muhammad Faraz Khalid, 3rd Year Student, *Allama Iqbal Medical College, Lahore*

Correspondence:
Muhammad Faraz Khalid, E-mail: mfaraz.khalid1@gmail.com

Submission Date: 31-12-2020
1st Revision Date: 14-12-2020
Acceptance Date: 20-12-2020

3) A factor intermediate between the independent and dependent variable cannot be a confounder

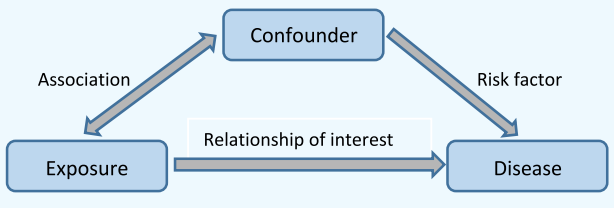


Fig 1: *Properties of a Confounder*

UNDERSTANDING THROUGH EXAMPLES

1) In a hypothetical experiment we tried to compare the effect of drug A, used in more severe form of a disease, with that of drug B used in less severe variant of the same disease and found that drug B depicted better control of the disease. In the given condition the severity of the disease being studied will act as a confounder, which if not assessed while plotting the experimental design, can drastically affect the results. Since the severity range of the disease under study was not the same for the drugs A and B, the basis for their comparison can't be the same and therefore the results won't show the actual relation between the exposure (the drug) and the outcome (disease management)
2) In a study we try to find out whether utilization of caffeine before a test helps the students perform better in their exam as compared to non-caffeine users. The results showed that students who consumed caffeine before their test performed far better than those who didn't take caffeine. This type of experimental design is poor since it does not exclude the effects of confounders in the study. There might be a possibility that the students whose performance was poor did not have adequate sleep the night before the test or probably their level of preparation was not up to the mark. So these factors can act as confounders here.

DEALING WITH CONFOUNDING BIAS

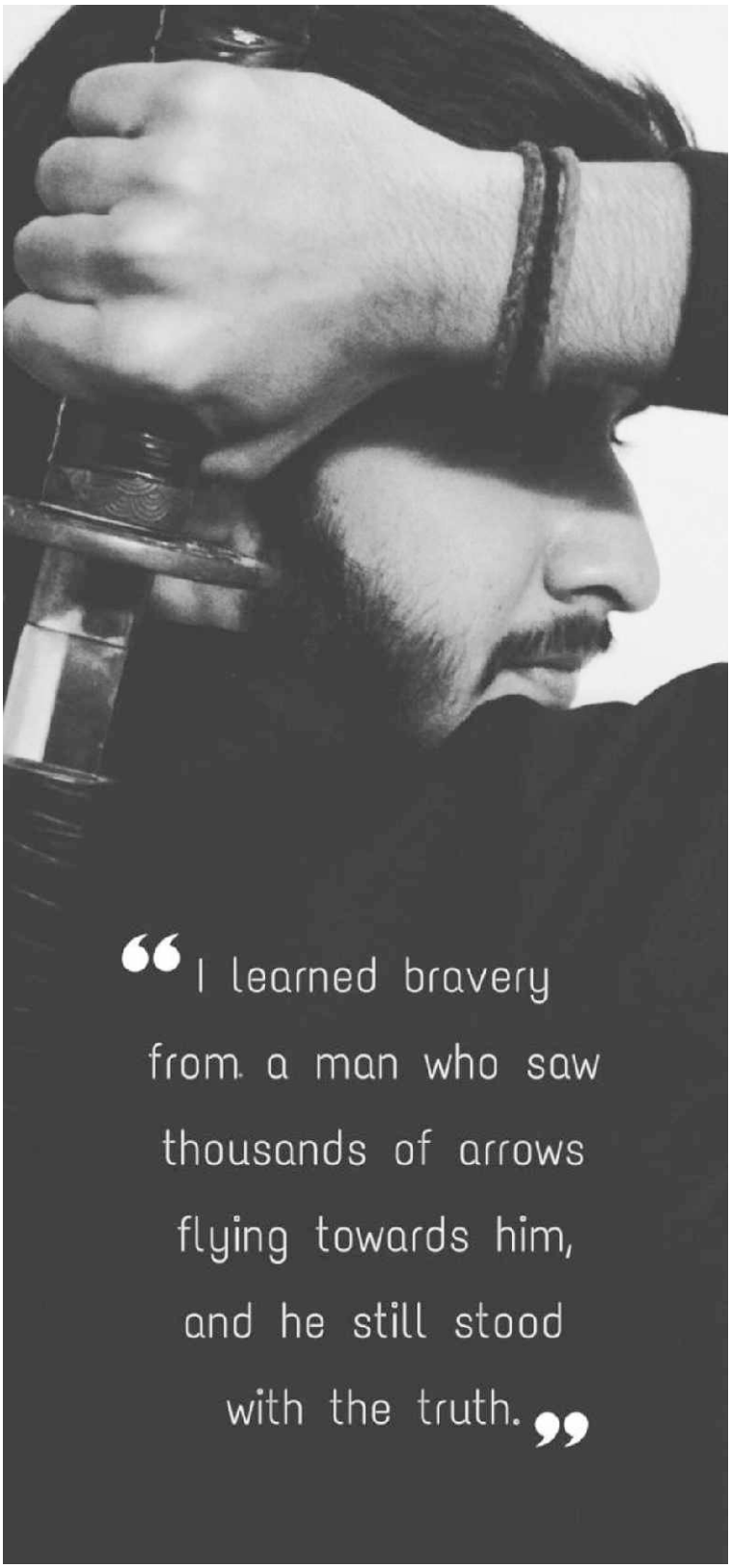
The effect of confounders on the variables can be reduced by taking following measures:

1) Identifying, measuring and reporting all the potential confounding variables in the study
2) Including only the subjects with same potential confounders (for example, age, weight, comorbidities) so that their net effect on the end result is minimal
3) Random sampling
4) Introducing control groups/variables
5) Within subject design of the study
6) Obtaining an "adjusted" estimate

An "adjusted" estimate means the effect of the exposure on the outcome when the effects of confounder have been withdrawn. On the other hand, a "crude" estimate includes the confounder influence as well. The magnitude of the influence of a confounder on the mutual relation of the exposure (independent variable) and the outcome (dependent variable) can be assessed by the difference between the crude and adjusted estimate (which, if >10%, declares the adjusted effect to be more reliable than the crude one).[4]

REFERENCES

1. Confounding [Internet]. En.wikipedia.org. 2020 [cited 5 November 2020]. Available from: https://en.wikipedia.org
2. Glen S. Confounding Variable: Simple Definition and Example - Statistics How To [Internet]. Statistics How To. 2020 [cited 6 November 2020]. Available from: https://www.statisticshowto.com/experimental-design/confounding-variable
3. Kamangar F. Confounding variables in epidemiologic studies: basics and beyond. Arch Iran Med. 2012 Aug;15(8):508-16.
4. Skelly A, Dettori J, Brodt E. Assessing bias: the importance of considering confounding. Evidence-Based Spine-Care Journal. 2012;3(01):9-12.
5. Jager K, Zoccali C, MacLeod A, Dekker F. Confounding: What it is and how to deal with it. Kidney International. 2008;73(3):256-260.
6. Pourhoseingholi MA, Baghestani AR, Vahedi M. How to control confounding effects by statistical analysis. Gastroenterol Hepatol Bed Bench 2012; 5(2): 79-83.
7. Brookhart M, Stürmer T, Glynn R, Rassen J, Schneeweiss S. Confounding Control in Healthcare Database Research. Medical Care [Internet]. 2010 [cited 7 November 2020];48:S114-S120.



Photograph by: Ali Rizvi