EFFECT OF PREOPERATIVE ADMINISTRATION OF DUTASTERIDE ON REDUCING BLOOD LOSS IN PERIOPERATIVE PERIOD OF TRANSURETHRAL RESECTION OF PROSTATE

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Abstract

Background and Objective: Clinical benign prostatic hyperplasia (BPH), a condition that commonly occurs in aging men. It is characterized by the development of lower urinary tract symptoms (LUTS), which can lead to impairment of bladder function and potential renal complications. TURP is the gold standard surgical treatment of BPH. Dutasteride is a 5-reductase and is used for medical management. This study was planned to ascertain the effect of pre-treatment dutasteride in reducing blood loss in patients undergoing transurethral resection of prostate (TURP).

Methods: It was a randomized clinical trial carried out at Department of Urology, Jinnah Hospital Lahore in which the total study sample was divided in two groups. One group received dutasteride and the second group was the control group. The study variables were Haemoglobin and Hematocrit values, clotting profile PT and INR, serum Ca levels and uric acid, BMI, prostate volume, residual volume of urine and hospital stay. Results were presented as mean ± SD or frequency (%). The main study outcome variable was mean blood loss (calculated by change in hemoglobin and hematocrit level).

Results: 6 (10.3 %) patients needed blood transfusion in dutasteride group and 7 (12 %) in control group (p=0.14). Post-surgery change in haemoglobin and HCT levels were less in dutasteride groups as compared to the control group (ΔHb 1.94±1.27 g/dL vs. 2.16±0.73 g/dL, respectively, p=0.02; ΔHct 5.68 % ± 2.56% vs. 6.52 % ± 2.39 %, respectively, p = 0.04).

Conclusion: The present research suggests that administering Dutasteride four weeks prior to the TURP procedure results in a decrease in blood loss during the peri-operative period, ultimately leading to improved patient outcomes.

Key words: Benign Prostatic Hyperplasia (BPH). Transurethral resection of Prostate (TURP), 5 Alpha Reductase Inhibitor (5-ARI)

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Benign prostatic hyperplasia (BPH) is a medical condition characterized by the enlargement of the prostate gland, resulting in urinary and urethral obstruction. This obstruction can cause varying degrees of bladder outlet obstruction (BOO), which can potentially harm the bladder and kidneys. The severity of symptoms depends on the size and location of the prostate adenoma.[1,2]

Although the progression of BPH is slow, some men may not experience any symptoms, while others may exhibit painless gross hematuria or elevated Prostate-specific antigen (PSA) levels. The incidence of BPH increases with age, with 50% of men developing microscopic disease by the age of 60 and 90% by the age of 85.[3] BPH results from the proliferation of both stromal and epithelial cells under the influence of sex hormones.[4] Immutable risk factors include age, genetics, and race; while modifiable risk factors include sex hormones, lifestyle, diet, obesity, and metabolic syndrome.[5] BPH

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also has a familial predisposition, with a six-fold increased risk in individuals with a positive family history.[6]

Benign Prostatic Hyperplasia (BPH) is a non-fatal condition, yet it can cause severe mental and physical health deterioration, significantly impacting a person's quality of life.[6] The International Prostate Symptoms Score (IPS and the quality of life (QoL) index are tools used to evaluate the severity of BPH symptoms, with the QoL index being a more critical measure and a score of 3 or higher considered problematic.[4]

Intravesical prostatic protrusion (IPP) measurement is a useful office diagnostic tool for predicting clinical BPH with 100% positive predictive value and specificity.[1] Prostate-specific antigen (PSA) levels below 1 µg/L can aid in differentiating patients with no clinical BPH, prostatitis, or prostate cancer.[7,8]

For patients with low-grade clinical disease, lifestyle modifications, fluid adjustment, diet, and exercise advice may be sufficient, while those with more advanced disease may require more aggressive medical or surgical treatment options depending upon urodynamic studies in advanced cases.[9]

Treatment options for BPH include lifestyle modifications, conservative management, and surgical resection of the prostate. Indications for intervention include refractory urinary retention, recurrent infections, upper urinary tract deterioration, and bladder stones. Various open and endoscopic procedures are available for treating BPH, depending on the prostate size, surgeon's ability, and experience. Transurethral resection of the prostate (TURP) is currently the gold standard treatment for patients with moderate to severe urinary tract symptoms, offering significant improvements in voiding symptoms, shorter hospitalization, and fewer complications.[10,11]

Perioperative complications of TURP include sepsis, shock, post-TURP syndrome, and haemorrhage. Although TURP is an established procedure, significant intraoperative and postoperative bleeding, remains a common complication leading to postoperative clot retention, blood transfusion, return to the operating room, and prolonged hospital stay.[12] Finasteride and Dutasteride are 5 alpha-reductase inhibitors that are used in the management of BPH.[13]

Dutasteride inhibits both types 1 and 2 isozymes of 5alpha-reductase, the enzyme responsible for converting testosterone to dihydrotestosterone in the prostate and other tissues.[14] In addition, Dutasteride reduces the vascularity of the prostate ,thereby reducing the incidence of perioperative Haemorrhage, reduces microvascular density in the bladder neck side of the prostate, and significantly decreased risk of perioperative prostatic urethral bleeding. The side effects of dutasteride include decreased libido, ejaculation disorders, testicular pain, and swelling. Short-term pre-treatment with finasteride and dutasteride significantly reduces perioperative bleeding during TURP and has minimal impact on sexual dysfunction.[15]

In addition, Kravchick et al. and few other studies reported that dutasteride may exert similar effects to reduce the vascularity of the prostate.[16] However, other studies have not reported that the pre-operative use of 5ARIs provides significant benefits concerning the prevention of hemorrhagic events in patients undergoing TURP.

Thus, this is the first prospective, randomized, clinical trial designed in our population to determine the effectiveness of pre-treatment with dutasteride in reducing blood loss in patients undergoing TURP.

METHODS

It is a randomized control trial in 116 patients who underwent transurethral resection of the prostate for enlarge prostate admitted in urology ward, Jinnah Hospital Lahore over a period of July 2022 to July 2023. Male patients aged above 45 years and having symptomatic BPH were included in the study. Patient with bleeding diathesis or on anti-coagulation therapy, chronic renal and hepatic insufficiency and patient having previous history of prostatic surgery were excluded. Patients with Hb < 12g/dL, PSA > 4ng /dL and severe cardio-pulmonary risk for surgery were also excluded from the study. The subjects were enrolled using non-probability consecutive sampling technique.

These patients were divided randomly into two groups by the simple lottery method. Group A included 58 patients undergoing transurethral resection of the prostate for enlarge prostate and given pre-treatment of 0.5mg /day dutasteride for 4 weeks. Group B had 58 patients undergoing transurethral resection of the prostate for enlarge prostate who were dutasteride naive. The subjects were enrolled in the study using non-probability consecutive sampling technique.

A comprehensive investigation of medical history, clinical and demographic variable was carried out, which include age, preoperative prostate volume, serum prostate-specific antigen (PSA) levels, hemoglobin (Hb) levels, hematocrit (Hct) levels, platelets count, activated partial thromboplastin time (APTT), international normalized ratio (INR) were recorded, and pelvic ultrasonography (USG) was done. Hb and Hct levels were also recorded within the first 24 hours after surgery. It was also noted if any kind of blood transfusion was done. The amount of blood loss was calculated. The primary study endpoint of the study was blood loss (change in hemoglobin and hematocrit level). The secondary endpoints were resected volume and hospital stay.

All the data were entered and analyzed using SPSS version 21. Normality distribution was evaluated. Numeric variables were presented as mean±SD as the data was normally distributed. Frequencies and percentages were calculated for categorical variables. Independent sample t-test was applied to compare variables e.g., age, prostate volume, PSA level, INR, and blood loss. A p-value of ≤0.05 was considered as statistically significant.

RESULTS

The patients from both groups were matched for demographical features and co-morbidities as no significant difference was observed for any variable (Table 1). The mean age of patients receiving dutasteride was 65.65 ± 6.64 and those of controls was 66.72 ± 6.32 (p=0.34). The mean BMI was observed as 28.12 ± 7.6 for dutasteride and 27.34 ± 8.5 for control group. There was no significant difference observed with regard to co-morbidities in both groups; diabetes (p = 0.33) and hypertension (p = 0.41).

Frequency distribution of lower urinary tract symptoms that BPH patients present is shown in (Table 2). 105 (90 %) patients reported to suffer from poor stream, 64 (55.1%) from flank pain, 85 (73.2 %) from dysuria, 93 (80.1 %) and 90 (77.5 %) from incomplete emptying and hesitating to urinate, respectively.

No significant differences regarding volume of the prostate, PSA, age and resected prostate volume were observed among the two groups. Additionally, no side effects that occur after the operations like acute urinary retention resulting by blood clot or TUR syndrome occurred. The two study groups demonstrated similar levels of PT (p = 0.75), aPTT (p = 0.40) and INR (p = 0.47) upon their checkup one day prior to the surgery (Table 3).

Table 1: *Demographic characteristics of patients of control and dutasteride group*

Variables	Group A (Dutasteride) n = 58	Group B (Control) n = 58	p - value
Age (years)	65.65 ± 6.64	66.72 ± 6.32	0.34
BMI (kg/m²)	28.12 ± 7.6	27.34 ± 8.5	0.21
Co-morbidities			
Diabetes mellitus	8 (13.7 %)	6 (10.3 %)	0.33
Hypertension	11 (18.9 %)	13 (22.4 %)	0.41

Data was expressed at mean ± S.D and frequency (%)

Table 2: *Sign and Symptoms of patients presented with BPH*

Variable	N (%)
Symptoms	
Poor stream	105 (90 %)
Flank pain	64 (55.1 %)
Dysuria	85 (73.2 %)
Incomplete emptying	93 (80.1 %)
Straining	90 (77.5 %)

Data was expressed as frequency (%)

Transfusion was needed in 6 (10.3 %) patients in dutasteride group and 7 (12 %) patients in control group (p=0.14). Hb and Hct declined more in control group than in dutasteride group after surgery (ΔHb 1.94 ±1.27 g/dL vs. 2.16±0.73 g/dL, respectively, p=

Table 3: *Urinary system parameter and blood parameters of patients of both groups before TURP*

Variable	Group A (Dutasteride) n = 58	Group B (Control) n = 58	P-Value
Urinary system parameters			
Prostate volume (g)	61.02 ± 29.49	59.17±35.08	0.70
PSA (ng/mL)	6.48 ± 8.98	6.05 ± 21.31	0.92
Residual urine (ml)	84.17 ± 61.87	63.78±55.77	0.12
Blood parameters			
Hb (before TURP) (g/dL)	13.83 ± 1.58	13.89 ± 1.56	0.87
Hct (before TURP) (%)	40.58 ± 4.44	40.82 ± 4.82	0.87
PT (s)	11.35±1.00	11.41 ± 1.01	0.75
aPTT (s)	30.61 ± 4.27	31.25 ± 3.07	0.40
INR	0.93 ± 0.82	0.95 ± 0.72	0.47

PSA: Prostate-specific antigen; Hb: Hemoglobin;
Hct: Hematocrit; PT: Partial thromboplastin time;
aPTT: activated partial thromboplastin time;
INR: international normalized ratio;
TURP: Transurethral urinary resection

Table 4: *Urinary system parameter and blood parameters of patients of both groups after TURP*

Variable	Group A (Dutasteride) n = 58	Group B (Control) n = 58	P-Value
Resected Prostate volume (g)	24.8 ± 16.76	23.81±14.21	0.73
Hospital stay (days)	3.96 ± 1.08	4.77±1.18	0.01*
Residual urine (after TURP)	18.07 ± 15.45	11.47±24.68	0.14
Hb (after TURP) (g/dL)	12.95±1.31	12.78±1.12	0.02*
ΔHb (after TURP)/ blood loss	1.94 ± 1.27	2.16 ± 0.73	0.02*
Hct (after TURP) (%)	37.8 ± 3.23	36.2 ± 3.12	0.01*
ΔHct (after TURP)	5.68 ± 2.56	6.52 ± 2.39	0.04*

Δ:Delta (change or difference)
**Statistically significant*

0.02; ΔHct 5.68 % ± 2.56% vs. 6.52 % ± 2.39 %, respectively, p = 0.04) (Table 4)

DISCUSSION

In men of advanced age, Benign prostatic hyperplasia exists as a commonly present condition.[17] Gland enlargement is the characterizing feature associated with BPH. Transurethral resection of the prostate (TURP) has been a choice of treatment of BPH. Still, TURP is the direct and the most obvious reason of surgical hemorrhage. Heavy blood loss due to the bleeding leads towards an increase in the risk of introducing hemodynamic disturbances, necessitating blood transfusion and generating immunologic consequences. Because of these reasons, need of blood transfusion during TURP, is considered its complication. There is also risk associated that massive hemorrhages may influence procedural outcome.[18]

The main objective of this study was to observe whether loss of blood during TURP could be reduced by administration of dutasteride for a short-term as a pre-operative treatment.

In our study, the mean age of patients suffering from BPH was 65.65 ± 6.64 years in the group getting dutasteride treatment and 67.72 ± 6.32 years for the control group. It varies from the study conducted by where the mean age was 71 years. They included 218 patients and studied the effect of dutasteride on BPH associated chronic hematuria. The variation may be due to the inclusion of more elderly population in the study.[19]

Loss of blood pertaining to the peri-operative procedures is amongst the most common complications associated with TURP leading to blood transfusion and clot retention in the immediate postoperative time. 5-Alpha reductase Inhibitors (5-ARI) is widely prescribed dihydrotestosterone (DHT) blocker medication to treat BPH and is usually given in combination with α-1 androgenic receptor blocker. Early studies on finasteride demonstrate its ability to reduce blood supply in the prostate and to reduce mean vascular density. Hence the evidence of the advantageous use of 5-ARI in BPH treatment to reduce the blood loss.[20] It has been reported that usage of dutasteride for a period of 6 weeks to decrease the vascularity of prostrate has good results. There are plenty of studies that document the efficacy of dutasteride for managing gross hematuria.[21]

In our study, the mean of blood loss in the dutasteride group was 1.94 ± 1.27 and for the control group was it was 2.16 ± 0.73. Nonetheless, noted the mean change in pre-postoperative Hb in group receiving dutasteride treatment to be 1.81±0.71 g/dL compared to control group where it was 2.96 ± 0.80 g/dL.[22] Our patients showed no statistically significant difference

in the preoperative levels of hematocrit and hemoglobin in both of the groups. But levels of hematocrit and hemoglobin showed significant differences among the two groups in the post-operative period, yielding results in the support of our hypothesis. Another study demonstrated no reduction of statistical significance in the loss of blood following the use dutasteride for 7 – 14 days before TURP in comparison to placebo group. Despite that, the Pastore, Mariani[23] made an observation that dutasteride for longer periods will lead to the reduction of blood loss in postoperative and intraoperative periods when comparison to a short course.[23]

In our study the patients were followed up for 5 days. No heamaturia was observed up till 5 days in postoperative period. This is not a surprising finding as dutasteride blocks the two-isoenzyme associated with 5α reductase. Hence leads to complete inhibition of 5α reductase.

The mechanism of apoptosis, to shrinking of prostate as the primary mechanism of action associated with 5ARIs fails to explain with certainty the rapid reduction of hematuria in the prostate in under 5 days. That can be explained by the shrinking of the prostate only resulting in after the use of 5ARIs for around 6 months.[10]

The rapidity of the response achieved upon the use of dutasteride for the treatment of acute hematuria may indicate that it targets some corresponding pathological condition which settles in a short duration. The said condition might be inflammation. Therefore, it is thought that by introducing an anti-inflammatory effect, dutasteride stops the acute hematuria while for the inhibition of recurrent hematuria the possible mechanism of action is thought to be apoptosis in the vascular prostates and inhibiting angiogenesis. An editorial viewpoint on the work done, attributes the rapid response for reducing extravascular edema is through reduced production of VEGF. VEGF is a type of vasodilator thought to have nearly 50,000 more potency comparable to that of histamine.[12]

Besides that, one study also noted that patients belonging to the control group to have significantly longer duration of hospital stay similar to the results published by Our study demonstrated significantly reduced postoperative and perioperative bleeding in group of patients who received dutasteride for the duration of 2 week prior to their TURP.[19] No significant difference was noted on the resected prostate volume. Coagulation levels were analyzed by us prior to TURP so that the effect of dutasteride on controlling the bleeding can be assessed. INR, PTT and aPTT showed no statistically significant differences among the two study groups and on the basis of obtained results, vas-cularity related bleeding resulting in during TURP may be the only factor affected by dutasteride.

There are a few limitations of the study. It is a single center study. Moreover, patients were followed up only for 5 days so information regarding long term outcomes is missing. Further research based on comparing the impact of dutasteride to be consumed for different time periods, i.e., 2 weeks, 4 weeks, and 6 weeks and long term follow ups should be conducted.

CONCLUSION

The present research suggests that administering Dutasteride four weeks prior to the TURP procedure results in a decrease in blood loss during the perioperative period, ultimately leading to improved patient outcomes.

Ethical Approval:

The Ethical Approval for this study was obtained from Allama Iqbal Medical College Lahore. (Reference No. 67th/ERB).

Conflict of Interest *None*

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