COMPARATIVE STUDY OF RIVAROXABAN WITH ENOXAPARIN AS THROMBO PROPHYLAXIS IN TOTAL HIP REPLACEMENT

Muhammad Zafar Iqbal Shahid,[1] Muhammad Khalid,[2] Tanveer Haider,[3] Muhammad Siddique Hamid,[4] Muhammad Khalid Syed,[5] Asim Islam[6]

Abstract

Background and Objectives: In total Hip arthroplasty, thromboembolism prophylaxis is a standard practice with minimal recommended duration of ten days. Thromboembolism prevention leads to reduction in symptomatic venous thromboembolic complications without risk of major bleeding.To assess and compare the efficacy of oral rivaroxaban with subcutaneous enoxaparin for prevention of thromboembolism after total hip and total knee replacement.

Methods: It was a Randomized Control Trial conducted at Department of Orthopedic Surgery, Services Hospital Lahore. After permission from the Institutional review board, a total number of 200 patients who underwent either total hip replacement (THR) were enrolled in the study. These patients were divided into 2 equal groups A and B, each group having 100 patients. In Group A, all the patients were given Rivaroxaban 10 mg daily while in Group B Enoxaparin 40mg s/c was given. In all the patients' anticoagulant prophylaxis was started 3-5 days before the surgery and 7-10 days after the surgery during Hospital stay.

Results: In group A where all patients were given Tab Rivaroxaban 10mg daily, did not show any signs of DVT in the final follow up. In Group B, DVT occurred in 2 patients (2%) during the 1st week post operatively. This shows that Rivaroxaban causes lower incidence of thromboembolism when compared to enoxaparin.

Conclusion: Rivaroxaban showed better anticoagulant effects than enoxaparin. It has slight higher risk of bleeding than enoxaparin. Direct factor Xa inhibitors are effective to prevent thromboembolism after total hip and total knee replacement. The anticoagulant effects are not necessarily compromised with risk of high bleeding..

Key Words: Thrombo prophylaxis, Enoxaparin, Rivaroxaban, Hip Athroplasty, Knee arthroplasty.

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Venous Thromboembolism is a serious complication during and after hospitalization.[1] Without its Prophylaxis, thromboembolism ranges from 40-60% in major orthopedic surgery. Patients undergoing arthroplasty are at high rise of thromboembolism in the post-operative period and discharge from the hospital. Because of surgical trauma, twisting of joint during orthopedic surgery, long restraining of the limb and as a result of Traction results in injury to the veins. These further result in Thromboembolic complication.

According to American Heart Association Pulmonary embolism proved fatal in 10,000 patients and around 2 million Americans suffer from DVT each year. One of the strong predisposing factors for Pulmonary embolism are major surgeries like THR and TKR[2]. An extensile prophylaxis has been recommended for preventing venous thromboembolism in patients undergoing THR. Mostly this prophylaxis is recommended in patients during hospital stay and on discharge from the hospital. During this short duration of hospital stay,

1,2,4,5,6. Department of Othopedic Surgery Ameer ud Din Medical College/LGH, Lahore
3. Department of Orthopedic Surgery, Khawaja Safdar Medical College, Sialkot

Correspondence:
Muhammad Zafar Iqbal Shahid, *Department of Othopedic Surgery Ameer ud Din Medical College/LGH, Lahore*
Email: dr.zafar2014@gmail.com

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thromboprophylaxis results in reduced quantity of patients having thromboembolism. Almost 40-70% of the patients suffer from thromboembolic complications in THR who do not receive adequate prophylaxis against thromboembolism.[3]

Although the improved surgical techniques have reduced the risk of embolization.[4] Still there are chances of fatal embolization.[5] A lot of work has been done for prophylaxis and prevention of DVT,[6] Chemo prophylaxis has got a significant role in preventing DVT in orthopedic surgery.[7] Several studies suggest that Thrombo prophylaxis after joint replacement leads to reduction in thrombo embolic complications especially the risk of major bleeding.[8]

Several studies suggest that thromboprophylaxis after joint replacement leads to reduction in thromboembolic complications especially DVT and Pulmonary embolism.

Thromboembolic Prevention can be divided into two types; mechanical and pharmacologica.[9] These are mobilization, intermittent pneumatic compression devices, graduated compression stockings and Venous foot pumps.[10] Pharmacological Preventions are Aspirin, Heparin in un-fractioned form, LMWH, vitamin K antagonists,[11] synthetic penta saccharide factor XA inhibitor like fondaparinux and direct inhibitors of factor XA like rivaroxaban.[12]

Rivaroxaban is a direct inhibitor of factor XA. In July 2011,[13] it was used to prevent DVT in patients undergoing knee and hip arthroplasty.[14] In November 2011 it was approved by FDA to prevent stroke in patients with common type of abnormal healthy rhythm. For the last 3 years. It has been used as an anticoagulant in patients with COVID-19.

In a study done by Erickson et al showed Major venous thromboembolism occurred in 4 of 1686 patients (0.2%) in the rivaroxaban group and in 33 of 1678 patients (2.0%) in the enoxaparin group (absolute risk reduction, 1.7%; 95% CI, 1.0 to 2.5;15 P<0.001). Major bleeding occurred in 6 of 2209 patients (0.3%) in the rivaroxaban group and in 2 of 2224 patients (0.1%) in the enoxaparin group (P=0.18).[16]

Rivaroxaban inhibits both free and clot bound factor Xa as well as Prothrombinase activity. In this way it prolongs the clotting time. It is 10,000 times more selective for factor Xa than other related serine proteases.[17]

If the anticoagulant monitoring or its dose adjustment is required then the functional antifactor XA Chromogenic assessment is used. In this assessment one has to use plasma spiked with rivaroxaban for creation of a standard curve. The plasma protein binding for rivaroxaban is 90%-95% and serum albumin is the main circulating binding product. Rivaroxaban is advantageous in the sense that it does not require the strict monitoring. The antidote for rivaroxaban is andexanet alpha (Andexxa) and can be given if increased bleeding occurs with rivaroxaban[18]. Evidences suggest that 10mg dose of Rivaroxaban is effective to prevent thromboembolism in patients with Total Hip or Total Knee arhtroplasty.[19]

The side effects of rivaroxaban are increased bleeding tendency, back ache, legs weakness, hemoptysis, difficulty in breathing and swallowing.

Low molecular weight heparin bound to antithrombin III can inactivate the factor IIA, IXA, XA and XIIA20. A lot of studies have shown that LMWH reduces the incidence of DVT in 70% of the cases.[21] These studies have confirmed that rivaroxaban has significant superiority as compared to enoxaparin in controlling thromboembolism. However, some studies have shown that rivaroxaban has increased risk of bleeding as compared to enoxaparin in patients with THR and TKR. Other studies suggest that no demonstrable differences are observed between rivaroxaban and enoxaparin in terms of major bleeding, venous thromboembolism and re operation after total hip and knee replacement.[22]

Methods

The prospective randomized clinical trial was carried out at department of orthopedic surgery services hospital Lahore. After permission from the Institutional review board of this Hospital a sample of 200 patients was calculated with 5% significance level, 80% power

of study, assumed proportion of Major venous thromboembolism occurred in 4 of 1686 patients (0.2%) in the rivaroxaban group and in 33 of 1678 patients (2.0%) in the enoxaparin group. A total number of 200 patients, 100 in each group was calculated using formula: n = (Zα/2+Zβ)2 * (p1(1-p1)+p2(1-p2)) / (p1-p2)2, where Zα/2 is the critical value of the Normal distribution at α/2 (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Zβ is the critical value of the Normal distribution at β (e.g. for a power of 80%, β is 0.2 and the critical value is 0.84) and p1 and p2 are the expected sample proportions of the two groups.

The patients underwent either THR for the last 03 years from Dec 2017 to Dec 2020 were included through a non-probability / purposive sampling technique for the study. Patients with coagulation disorder, previous history of thromboembolism and patients with poly trauma and head and spine injury were excluded from the study. All these patients were divided into 2 equal groups A and B randomly, each group having 100 patients. The age range was 30-70 years in both the groups(Mean 45+-7 years). In group A there were 60 males and 40 females. In 80 patients we performed THR and in 20 patients, TKR was done. In group B, there were 70 males and 30 females. THR was done in 90 patients while 10 patients underwent TKR. All these patients were operated under spinal anesthesia. A written permission was taken from each patient regards the anticoagulant prophylaxis. All these patients were admitted through emergency and OPD of orthopedic department. In Group A, all the patients were given oral Rivaroxaban 10 mg daily while in Group B Enoxaparin 40mg s/c was given once daily. In all the patients anticoagulant prophylaxis was started 3-5 days before the surgery and minimal of 10 days after the surgery. Before starting the anticoagulant prophylaxis, each patient had Hb level, platelets count, PT, APTT levels, INR and Renal profile.

The anticoagulant prophylaxis was omitted 12hrs before the surgery and was restarted 6-8 hours after the wound closure. Patient drain was removed on the 2nd post-op days when it contained less than 20 ml of blood per day. Both LMWH i.e enoxaparin and Rivaroxaban were continued for 2 weeks post operatively.

Each patient was mobilized 2-4 days (mean2+-1.5) post operatively and was discharged 5-7 days after the surgery. During the hospital stay major and minor post operative complications were recorded. Major post operative complications were defined as bleeding from the wound, intra peritoneal, intra cranial or intra spinal bleeding resulting in fall in Hb of more than 2g/dl. The minor complications were microscopic hematuria, bleeding per rectum and wound site hematoma.

Follow up: All patients in both groups were followed weekly interval for further four weeks.

At each follow up these patients were assessed by Doppler's ultrasonography for DVT. The safety profile assessment which includes Hb level, platelets count and PT,APTT,INR and Renal profile were also carried out in these patients are at each follow up. During hospital stay both major and minor complications were recorded and compared with each other.

RESULTS

The age range in both groups was 30-70 years (mean:45+-7), each group having 100 patients. In Group A there were 60 males and 40 females, whereas in Group B there were 80 males and 20 females. Mean hospital stay was 6.5 +-3.5 days(5-12days) while mean operative time duration was 110(90-130min) minutes in group A and 120(90-150min) minutes in group B. No significant difference was found regarding the operative duration in both the groups($p<0.001$).

In group A, no patient showed signs of DVT in the final follow up. In Group B. DVT occurred in 2 patients (2%) during hospital stay post operatively. This shows that Rivaroxaban causes lower incidence of thromboembolism when compared to Enoxaprin (relative risk of 0.70 & 95% of confidence interval). Still shows that there is no significant difference regarding DVT in both of these groups($p<0.001$). No large Hematoma or bleeding episodes were reported in both groups except 7 patients in Group A had bleeding episodes in the 4th post op day. These 7 patients required blood transfusion up to 2 units in the post-operative period during the hospital stay (3 cases of hematuria

and 4 cases of bleeding from the wound, 16.59%). This bleeding tendency is still higher than in Group B where there were 02 cases of hematuria and 01 case of bleeding from the wound (p= 0.035).

In both of these groups, this resulted in fall in Hb of more than 2g/dl(2-4g/dl). In group A 5 (5.0%) patients required 02 units of blood transfusion while 02 (2.0%) patients require 03 units of blood transfusion for each of them. Hb level, platelets count and PT, APTT levels were also not different in both the groups (p>0.05). This indicates that prompt treatment for thromboembolism as a clear cut impact and rivaroxaban has clear safety in prevention of pulmonary embolism in patients undergoing arthroplasty.

In group B, 01(1.0%) patient required 02 units of blood transfusion while 01 (1.0%)patient required 03 units of blood transfusion. No patient required the re do surgery in both the groups.

Minor post operative complications were observed in 02 (2.0%) patients in group A at 3rd post op day. And in 1 (1.0%) patient in group B at 5th post op day which were insignificant(p<0.002).

Table 1: *Comparison of Complications in Group A Versus Group B*

Major Complications	Group A (n=100)	Group B (n=100)	P value
Bleeding leading to decrease in Hb	7 (7.0%)	2 (2.0%)	.050
Blood transfusion 2 units	5 (5.0%)	1 (1.0%)	0.002
More than 2 units	2 (2.0%)	1 (1.0%)	0.002
Treatment Discontinuation	0 (0.0%)	0 (0.0%)	-----

DISCUSSION

Patients undergoing arthroplasty have high risk of developing thromboembolic complications leading to increased chances of morbidity and mortality.[1] Many pharmacological agents are used as prophylaxis against DVT in patients undergoing arthroplasty,[2] With improved surgical techniques and with judicious use of anticoagulant therapy this risk can be minimized.[3]

In the Current study rivaroxaban and enoxaparin have provided excellent thromboprophylaxis after arthroplasty. There is absolute reduction in DVT, Pulmonary embolism and mortality from embolism. No difference was reported in Hb level, blood in the drain, coagulation profile, wound complications, bleeding from the wound and DVT in rivaroxaban group when compared with enoxaparin group.

Although there is slight increase in incidence of bleeding in patients with rivaroxaban but still major bleeding episodes are uncommon with this drug.[6]

A lot of studies are consistent with our findings regarding the safety and efficacy of oral Rivaroxaban in comparison with enoxaparin for prevention of DVT,[9] pulmonary embolism and venous thromboembolism in patients undergoing THR and TKR.[10]

In a study conducted by Xie J et al, they came to the conclusion that both rivaroxaban and enoxaparin are effective in thromboembolism prevention.[12] There was no risk of major or clinically relevant bleeding.

W.Beyer et al in his study regarding the effectiveness of rivaroxaban in prevention of pulmonary embolism in patients undergoing arthroplasty. They came to the conclusion that non-vit K antagonists oral anticoagulants like rivaroxaban has been proved to have superior efficacy for thromboprophylaxis when compared with Enoxaparin. It has similar safety to all tested regimes of enoxaparin in phase III clinical studies of venous thromboembolism prevention in elective total hip replacement.[13]

In another study conducted by Runner RP et al in thromboembolism prevention after arthroplasty, came to the conclusion that oral anticoagulants decrease the incidence of thromboembolism after hip or knee replacement procedures. Furthermore, no serious complication occurred after oral rivaroxaban. He suggested that rivaroxaban offers an attractive alternative to other anticoagulants.[14]

J. Liu et al conducted a meta-analysis to determine the efficacy and safety of rivaroxaban after total hip and knee replacement. He came to conclusion that rivaroxaban has more superior effects as compared to enoxaparin for thromboprophylaxis when used in patients with THR.[1]

In the study conducted by F.H. Haung et al, they came to the conclusion that rivaroxaban has significantly lower risk of venous thromboembolism as com-

pared to enoxaparin. There is also no increase in major bleeding risks in both of these groups.[16]

In a Meta Analysis Ning GZ. et al. Came to the conclusion that rivaroxaban was not associated with increase in all-cause mortality and it is more beneficial than enoxaparin for preventing symptomatic DVT.[17] All these studies reveal that although there is slight risk of bleeding complication with rivaroxaban but still rivaroxaban is as effective as enoxaparin in prevention of thromboembolic complications after arthroplasty.[18,19] In future Rivaroxaban may increase its preference for prevention of pulmonary embolism after total hip and knee replacement.[20] These also reveals that oral rivaroxaban provides greater ease for used compared with enoxaparin which is given subcutaneously.[21]

CONCLUSION

Direct factor Xa inhibitors are effective to prevent thromboembolism after total hip and total knee replacement. The anticoagulant effects are not necessarily compromised with slightly high risk of bleeding when compared with enoxaparin. Rivaroxaban showed better anticoagulant effects than enoxaparin. Rivaroxaban is potent and safe new compound which is taken orally for thromboembolic prophylaxis in patients undergoing major orthopedic surgeries like THR and TKR.

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REFERENCES

1. Manista Gc et al. Anticoagulants in Revision Total joint Arthoplasty: A Retrospective review of 1917 cases. Orthopaedics 2019 Nov 1; 42: 323-329
2. A. Shahi, A.F. Chen, T.L.Tan, M.G. Mattenfort, F. Kucukdurmaz, and J. Parvizi " the incidence and economic burden of in-hospital and venous thromboembolism in united states". The J arthroplasty;32(4): 1063-1066
3. B. Stefano et al. Early Discharge And Home Treatment With Low Risk Pulmonary Embolism with Oral Factor Xa Inhibitors Rivaroxaban: an international multicenter single-arm Clinical trial. Eur Heart J 2020; 14(4):509-518.
4. Jenny JY, Papinger I, Samama CM. European Guidelines on perioperative Venous Thromboembolism Prophylaxis: Aspirin. Eur J Anaesthesiol 2018; 35(2) : 123-129
5. Cote MP, Chen A, Jiang Y, Chen V, Pulmonary embolism rate after Total Knee Arthroplasty even with prophylactic anticoagulants. J Arthroplasty 2017; 32(12): 3833-9
6. EINSTENI Investigators et al. Oral Rivaroxaban for Symptomatic Venous Thromboembolism. N Engl J Med 2010 ; 363(26): 2499-2510
7. DA Flevas et al. Thromboembolism prophylaxis in Orthopaedics: an update. EFORT Open Rev 2018; 31: 13-142
8. S Thiengwittayaporn, B. Nicolas et al. Asia-Pacific Venous Thromboembolism consensus in knee and hip Arthroplasty. Knee Surg & Relt Res 2021; 33(24)
9. Riksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med. 2008 Jun 26;358(26):2765-75.
10. Ander DR et al; American Society of Hematology 2019 guidelines for management of Venous Thromboembolism: Prevention of Venous Thromboembolism in surgical hospitalized patients. Blood Adv 2019; 3(23): 3898-3944
11. Wendelboc AM, Raskob GE. Global burden of Thrombosis: Epidemiological Aspects. Circ Res 2016; 118: 1340-1347
12. Xie J, Maj, Huang Q et al. Comparison of Enoxaparin and Rivaroxaban in balance of antifibrinolysis and anticoagulation following total knee replacement. A pilot study. Med Sci Mmit 2017; 23:704-11.
13. W-Beyer, P Mouret, AGG Turpie; Rivaroxaban for Venous thromboembolism prevention after major Orthopaedic Surgery: Translating Trial Date into routine clinical practice. Orthop Res & Rev 2017; 9: 1-11
14. Runner RP et al. utilization, pattern, efficacy and complication of Thromboembolism Prophylaxis Strategies in primary hip and knee Arthroplasty as reported by American Broad of orthopaedic Surgery. J Arthroplasty 2019; 34(4): 729-734
15. J Liu et al; effectiveness and safety of Rivaroxaban for prevention of thrombosis following Total hip or knee replacement: a systematic review and meta analysis. Medicines 2019: 98-9
16. F.H. Haung et al. Rivaroxaban vs Enoxaparin for prevention of thromboembolism after total knee arthroplasty, a meta analysis. Medicine : Nov 2018 vol 97 issue 48 Pe 13465.
17. Ning GZ, Kan SL, Chen Lx et al. Rivaroxaban for thrombo prophylaxis after Total hip or Knee arthro-

plasty: a meta analysis with trial sequential analysis of randomized control trials. Sci Rep 2016;6:23726.

18. Momin J. H. Candidate P; Hughes G. J. Andexanet alfa (Andexxa) for reversal of direct anticoagulants. Pharmacy and Therapeutics 2019; 44: 530-549
19. Cao YB, Zhang JD, Shen H et al. Rivaroxaban versus Enoxaparin for Thrombo prophylaxis after total hip or knee arthroplasty : a meta analysis of randomized controlled trials. Eur J Pharmacol 2010;66:1099-108.
20. L. R Jay and B. A. Jennifer(Jay R. libarman) venous Thromboprophylaxis after Total Hip & Knee arthroplasty. J Bone Joint Surg (Am) 2021; 103(16) : 1556-64
21. Turun,S,;Banghua, L; et al. A systematic review of rivaroxaban versus enoxaparin in prevention of venous thromboembolism after hip or knee replacement. Thromb.Res.2011;127:525-534.
22. Hur M, Park SK, Koo ch, et al. Comparative efficacy and safety of anticoagulants for prevention of venous thromboembolism after Hip and Knee arhtroplasty. Acta orthop 2017; 88:634-41.