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ASPIRIN VS RIVAROXABAN FOR VENOUS THROMBOEMBOLISM PROPHYLAXIS AFTER HIP OR KNEE ARTHROPLASTY: RANDOMIZED COMPARATIVE STUDY

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Abstract

Background : Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant postoperative complication following hip or knee arthroplasty. Effective prophylaxis is essential to prevent these complications, and various anticoagulants, including aspirin and rivaroxaban, are commonly used for this purpose. Despite their widespread use, there is ongoing debate regarding the optimal agent for VTE prophylaxis in this setting.

Aim and Objective : This study aimed to compare the efficacy and safety of aspirin versus rivaroxaban in the prevention of VTE after hip or knee arthroplasty.

Material and Methods : A randomized, comparative study was conducted at Mahatma Gandhi Medical College & Hospital, Jaipur, from July 2022 to December 2023. A total of 100 patients undergoing elective primary or revision hip or knee arthroplasty were included in the study. Participants received rivaroxaban (10 mg daily) from postoperative day 1 to day 5. Thereafter, they were randomized to continue either aspirin (75 mg daily) or rivaroxaban (10 mg daily) for an additional 9 days (knee arthroplasty) or 30 days (hip arthroplasty). The primary outcome was the incidence of VTE, confirmed by clinical examination and imaging. Secondary outcome included bleeding complications.

Results : Both aspirin and rivaroxaban were effective in preventing VTE, with no significant differences between the groups. The suspicion of VTE was similar in both groups, but imaging was normal in all suspected patients. Bleeding complications were also comparable between the two treatment regimens.

Conclusion : Aspirin is as effective and safe as rivaroxaban for VTE prophylaxis after hip or knee arthroplasty. Given its cost-effectiveness and similar safety profile, aspirin presents a viable alternative to rivaroxaban for postoperative VTE prophylaxis in these patients.

Keywords : Venous thromboembolism, aspirin, rivaroxaban, hip arthroplasty, knee arthroplasty, randomized study

INTRODUCTION

A serious and sometimes fatal complication that frequently arises during and after hospitalisation is venous thromboembolism (VTE). Additionally, it has a major role in perioperative mortality as well as unplanned hospital deaths.[i] The incidence of DVT after

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THA, TKA, and Hip Fracture Surgery (HFS) without the use of medication to prevent blood clot formation was found to be 41% in a recent epidemiological study conducted at 19 orthopaedic centres in seven Asian countries.[ii] The incidence of total DVT and proximal DVT was highest among patients who underwent TKA, with rates of 58.1% and 17.1% respectively. This was followed by patients who underwent hip fracture surgery (HFS), with rates of 42.0% and 7.2% respectively. The occurrence rate of proximal DVT in individuals who did not receive preventative treatments following hip fracture surgery (HFS) was 15.7%.[iii] Prior research has indicated that, in the absence of any preventive measures, Pulmonary Embolism (PE) accounts for 5%–10% of mortality among hospitalised patients. The occurrence of PE in inpatient fatalities was observed to be 2%–3% following elective hip arthroplasty and 4%–7% after hip fracture surgery.[iv,v,vi]

A triple thrombotic event occurs when venous stasis, hypercoagulability, and endothelial injury coincide, resulting in the formation of thrombi. Common risk factors for deep vein thrombosis include prolonged immobility exceeding 72 hours, undergoing surgeries lasting over 2 hours, having a malignancy, being overweight, or experiencing other medical conditions..[vii] Predicting and preventing post-operative deep vein thrombosis by giving prophylaxis to patients who have been classified as high-risk due to certain risk factors is a critical component of patient care.[viii] Individuals who have undergone a significant surgical procedure are susceptible to developing deep vein thrombosis. Doppler ultrasonography is a diagnostic technique used to detect deep vein thrombosis. It is a non-invasive, cost-effective, and easily replicable procedure, which makes it advantageous in every aspect. The sensitivity and specificity for detecting proximal DVT are similar to those of venography, and there are no associated risks with its use.

Currently, there is no agreement on the optimal pharmaceutical method of prophylaxis. The most often utilised medications include Enoxaparin, a low molecular weight heparin (LMWH), and Rivaroxaban, a factor Xa inhibitor. However, the successful prevention of venous thromboembolism (VTE) is linked to a higher occurrence of certain complications after surgery, such as hematomas, superficial and deep infections, as well as systemic complications such bleeding from the nose, gums, and inside the skull..[ix , x] Rivaroxaban is associated with a higher risk of hemorrhagic events and wound complications than LMWH, despite having similar anti-thrombotic activity. A multicenter, double-blind, randomised experiment found that between 30% and 80% of patients had symptomatic DVT. Nonetheless, asymptomatic DVT occurred between 0.5% and 4% of the time.[xi]

The efficacy of Aspirin as a prophylactic treatment for VTE following TKA and THA has been well documented. However, its regular usage as the preferred medicine is still a subject of debate. A recent study has demonstrated that aspirin is a highly effective agent for preventingVTE. Compared to more aggressive anticoagulants, aspirin carries a lower risk of complications such as surgical wound secretion, bleeding, re-hospitalization, re-operation, periprosthetic infection, and even mortality.[xii]Some recent studies have highlighted another advantage of aspirin: its cost-effectiveness in comparison to LMWHs..[xiii]In the Huang et altrial,[xiv]which examined patients who got both medications for 21 days as part of a DVT prophylaxis. Based on the effectiveness of the two medications, aspirin and rivaroxaban had respective effectiveness rates of 83.3% and 84.9%. Aspirin and rivaroxaban have been demonstrated in studies to be useful in preventing DVT, however the evidence is still preliminary and lacks consistency.[xv,xvi]

Rivaroxaban is an orally administered drug that specifically targets and blocks factor Xa, a key component in the blood clotting process. It competitively inhibits both free and bound factor Xa, as well as prothrombin activity. As a result, it efficiently and safely prevents

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the formation of deep vein thrombosis.[xvii] Recently, it has been widely utilised in many countries for its effective anticoagulant properties. Aspirin is an affordable, ubiquitous, and readily accessible antithrombotic medication. The effectiveness of aspirin in preventing cardiovascular and cerebrovascular ischemic illnesses has been established. However, the question of whether aspirin should be routinely used as a preventive medication for VTE following surgery remains a topic of debate.[16,xviii]

MATERIAL AND METHODS

A Hospital Based Randomized Comparative study was conducted at the Department of General Medicine & Department of Orthopaedics, Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan**.** Patients who underwent Knee and Hip replacements at Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan were the study subjects. We enrolled 100 patients who met both inclusion and exclusion criteria, who underwent Knee and Hip Arthroplasty at Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan during the period- from July 2022 to December 2023, after taking ethical clearance from Institutional Ethical Committee.

INCLUSION CRITERIA:

- All the patients who underwent elective unilateral primary or revision Hip or Knee arthroplasty
- Willing to participate in study
- Life expectancy of patient more than 6 months
- No history of Major bleeding , Aspirin allergy , Peptic ulcer disease , or significant Hepatic disease
- Age more than 18 years

EXCLUSION CRITERIA:

- Hip or Lower limb fracture in the previous three months
- Metastatic cancer
- Major surgical procedure within previous three months
- Expected requirement for major surgery within 90 day period post-arthroplasty
- Platelet count<1 lakh/µL
- Women of child bearing potential who were not abstinent or not using any appropriate contraception or were breast feeding throughout the study
- Chronic daily aspirin use at dose greater than 100mg/day

METHODOLOGY :

All the patients eligible in study received a dose of Rivaroxaban 10mg/day starting from postoperative day 1 uptill day 5. Patients undergoing Knee arthroplasty were then randomly assigned to receive additional 9 days of thrombo-prophylaxis with either 10 mg oral Rivaroxaban or 75 mg of Aspirin once daily from post operative day 6. Patients undergoing Hip arthroplasty were randomly assigned to receive additional 30 days once daily dose of Rivaroxaban 10 mg or Aspirin 75 mg starting from post operative day 6. All the patients were followed up once a month for three months. After 90 days, no screening was performed in asymptomatic patients but patients suspected for DEEP VENOUS THROMBOSIS underwent compression ultrasonography from common femoral vein to atleast trifurcation of Popliteal vein. Patients suspected for pulmonary embolism were planned to have CT pulmonary angiography or VP scanning of lung. Written and informed consent was obtained from all participants before enrolment into the study

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Intervention :
Does the study involve use of :
(A) Drug: Yes
Group-1 : Aspirin – 75 mg per oral route
Group-2 : Rivaroxaban – 10 mg per oral route
(B) Devices - No
(C) Vaccines- No

STATISTICAL ANALYSIS
The data collected was entered into MS Office Excel Worksheet. Appropriate statistical tests were used to find the Significant Association. P value < 0.05 was considered to be statistically significant. The data collected was analysed using SPSS software version 25. The data was expressed in terms of frequency and percentage. Mean and Standard Deviation (SD) were calculated for various parameters.

RESULTS

Table 1: below comprises the mean and standard deviation (SD) of baseline characteristics between the aspirin and rivaroxaban groups :

Baseline Characteristic	Aspirin Group (n=50)	Rivaroxaban (n=50)	p-value
Age (years)	59.96 ± 8.58	56.98 ± 11.08	0.13
WBC (*10^3/µL)	7.93 ± 2.15	7.74 ± 2.08	0.66
Hemoglobin (g/dL)	11.74 ± 1.73	11.23 ± 3.57	0.37
Platelets (*10^3/µL)	203.24 ± 68.93	213.82 ± 60.89	0.41
RBC (*10^6/µL)	4.47 ± 1.109	4.50 ± 1.105	0.908
S. urea (mg/dL)	31.770 ± 9.511	30.808 ± 10.97	0.64
S. creatinine (mg/dL)	0.77 ± 0.26	0.82 ± 0.28	0.31
S. uric acid (mg/dL)	5.97 ± 1.72	6.08 ± 1.63	0.74
TSB (mg/dL)	0.76 ± 0.27	0.77 ± 0.33	0.84
Direct bilirubin (mg/dL)	0.42 ± 0.18	0.39 ± 0.18	0.37
Indirect bilirubin (mg/dL)	0.34 ± 0.18	0.38 ± 0.24	0.34
SGOT (U/L)	29.15 ± 7.91	30.88 ± 9.93	0.3
SGPT (U/L)	29.86 ± 11.77	31.306 ± 11.55	0.53
S. ALP (U/L)	95.96 ± 28.01	99.850 ± 39.12	0.56
Blood loss (ml)	183.4 ± 116.13	217.4 ± 140.05	0.19

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(Plus–minus values are means ± SD. None of the between-group comparisons were significant at baseline.)

Interpretation: The given **Table 1** compares baseline characteristics including age, complete blood counts (WBC, hemoglobin, platelets, RBC), renal function tests (serum urea, serum creatinine, serum uric acid), liver function tests (TSB, direct bilirubin, indirect bilirubin, SGOT, SGPT, S. ALP), and blood loss between the aspirin and rivaroxaban groups. No significant differences were found between the groups for these baseline characteristics ($p > 0.05$).

Table 2: Genderwise comparison of the study

			Gender		Total
			Female	Male	
Groups	Group 1	N	28	22	50
		%	56.0%	44.0%	100.0%
	Group 2	N	21	29	50
		%	42.0%	58.0%	100.0%
Total		N	49	51	100
		%	49.0%	51.0%	100.0%

P value=0.16

Above **Table 2** shows : Males were 44% and females were 56% in group 1. Males were 58% and females were 42% in group 2. Comparison of gender and groups showed statistically non-significant results.

Table 3: Mobility status-wise comparison of the study

			Mobility status					Total
			POD1	POD2	POD3	POD4	POD5	
Groups	Group 1	N	13	25	10	1	1	50
		%	26.0%	50.0%	20.0%	2.0%	2.0%	100.0%
	Group 2	N	13	23	10	2	2	50
		%	26.0%	46.0%	20.0%	4.0%	4.0%	100.0%
Total		N	26	48	20	3	3	100
		%	26.0%	48.0%	20.0%	3.0%	3.0%	100.0%

P value=0.94

Above **Table 3** shows : Mobility status were almost similar in both groups which showed statistically non-significant results.

Table 4: Operative procedure

			Operative		Total
			THR	TKR	
Groups	Group 1	N	28	22	50
		%	56.0%	44.0%	100.0%
	Group 2	N	33	17	50
		%	66.0%	34.0%	100.0%
Total		N	61	39	100
		%	61.0%	39.0%	100.0%

P value=0.78

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Above **Table 4** shows : Total hip and knee replacement surgery showed statistically non-significant results among groups.

Follow up and DVT result screening :

During the study, one patient had surgical site bleeding on POD 6 before randomizing the group, so was excluded from our study. All patients included in our study, were followed up at first month, second month, and at the end of third month, for symptoms of DVT or PE. Only 5 patients exhibited symptoms indicative of DVT. Consequently, these patients underwent USG Doppler, but revealed no presence of DVT in any cases.

DISCUSSION

The concern of the Orthopedic community with cases of preventing Venous Thromboembolism (VTE) after orthopedic procedures is paramount.[xix] If preventive measures are not adopted, the incidence of deep vein thrombosis (DVT) can reach 60% and that of fatal pulmonary embolism, up to 1.5% within 90days after total knee arthroplasty (TKA).[xx] Currently, there is no consensus on the best strategy for VTE prophylaxis after knee and hip arthroplasty. This study aimed to compare Aspirin and Rivaroxaban for venous thromboembolism prophylaxis after hip or knee arthroplasty.

VTE is the most common cause of peri-operative hospitalization death, and its complications consume a large amount of medical resources.[xxi] Anticoagulant drugs have been shown to reduce postoperative mortality and complications associated with VTE.[xxii] They reasoned that aspirin, because of its efficacy, low cost, and well-established side-effect profile, was potentially a good choice for thrombo-prophylaxis after total hip or total knee arthroplasty or hip fracture surgery.[xxiii,xxiv] Rivaroxaban is the world's first oral inhibitor of factor Xa. It is used to prevent and treat venous thromboembolism and prevent stroke or systemic embolism in atrial fibrillation. It has advantages of convenient administration, rapid action, and low risk of drug interaction. The use of oral anticoagulants in the perioperative period, represented by rivaroxaban, seems to be in doubt.

In our study, mean age was 59.96 years in group Aspirin and 56.98 years in group Rivaroxaban. Males were 44% and females were 56% in group aspirin. Males were 58% and females were 42% in group rivaroxaban. In Jatoi FS et al study,[xxv] the aspirin group had a mean age of 58.87 years and rivaroxaban group had a mean age of 59.44 years. Women comprised 47.5% of the aspirin group, while males comprised 52.5% of the group. The rivaroxaban group had 80 persons, of which 55 were men (68.8%) and 25 were women (31.2%).

In our study, no statistically significant differences were observed between the groups regarding the incidence of blood loss, similarly to the recent meta-analysis by Drescher et al,[xxvi] which evaluated only randomized studies comparing aspirin with one or more anticoagulants, and concluded that aspirin efficacy is similar to that of other anti-coagulants regarding bleeding control and VTE incidence. Some studies have reported that aspirin is effective in preventing VTE and has a lower risk of complications when compared with other more aggressive anticoagulants.[19] Vul-cano et al.,[xxvii] in a study with 1947 patients undergoing TKA and THA, compared the use of aspirin in relation to warfarin for the incidence of VTE and bleeding; those authors observed rates of 1.2% and 0.3%, respectively, with aspirin use, and 1.4%and 1.6% with warfarin use (n = 1947).Therefore, the increased incidence of local or systemic bleeding is another concern in the use anticoagulants, and some studies have shown a possible lower risk of bleeding with aspirin. Several studies have

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concluded that the use of rivaroxaban when compared with other anticoagulants increases therisk of complications related to wound healing.[10,xxviii]

Aspirin is already considered to be an effective drug in the prevention of cardiovascular and cerebral ischemic diseases. The 2008 ACCP (American College of Chest Physicians) guide-line recommends the use of this drug after total arthroplasties. However, although recommendation for aspirin use in the2012 guideline is low (Grade 2C), the study have shown that, when used in patients considered to be of low risk for VTE, it may be effective and safe after total arthroplasties.[xxix]

In our study, Total hip and knee replacement surgery showed statistically non-significant results among groups. Aspirin and rivaroxaban were similarly effective for preventing venous thromboembolism after either total hip or total knee arthroplasty. There were no between-group differences in effectiveness in the subgroup of patients who were receiving long-term aspirin therapy, which suggests that there was no benefit of adding 75 mg of aspirin to either aspirin or rivaroxaban prophylaxis. However, there were suggestions of more major and clinically relevant non-major bleeding among patients in the long-term aspirin subgroup, particularly among those who had been assigned to the aspirin group and hence were receiving a second daily dose of aspirin prophylaxis.

In our study, both aspirin and rivaroxaban were effective in preventing VTE after THA and TKA. There were no significant differences in the incidence of major bleeding complications between the two groups. Thus, aspirin and rivaroxaban were equally efficacious and safe as per our study. While, the recent study published by Weitz et al,[xxx]which compares the efficacy and safety of rivaroxaban (10 mg/day and 20 mg/day) with aspirin in secondary prevention of VTE demonstrates the absolute superiority of the anticoagulant in reducing the incidence of thromboembolic events, without increasing bleeding. In addition, a recent meta-analysis has shown a benefit for prevention with rivaroxaban.[xxxi] However, the inclusion criteria are not all surgical patients. It is well known that perioperative period is a crucial period with a high risk of VTE event but also with high risk for bleeding on the operative zone. As a matter of fact, the American Association of Orthopaedic Surgery recommends aspirin as a chemoprophylactic drug for VTE in 2012.[xxxii] In addition, other recent studies have shown that aspirin did not differ statistically significantly from other anticoagulants used for VTE prophylaxis after THA and TKA.[xxxiii,xxxiv]

In our study, all patients were followed up at first month, second month, and at the end of third month, for symptoms of DVT or PE. Only 5 patients exhibited symptoms indicative of DVT. Consequently, these patients underwent USG Doppler, but revealed no presence of DVT in any cases. A large double-blind randomised control trial (n = 3,424) by Anderson et al. (2018),[24] with a follow-up of 90 days, found no difference in the prophylactic efficacy of aspirin when compared to rivaroxaban. They noted an incidence of VTE of 0.64% in the aspirin group compared to 0.70% in the rivaroxaban group (95%confidence interval [CI] = 0.55-0.66). However, they found the incidence of major and non-major bleeding to be higher in the aspirin group compared to the rivaroxaban group (1.29% vs. 0.99%; p-value = 0.43). This was, however, confounded by the fact that some trial participants were permitted to continue their usual dose of aspirin in addition to the randomised prophylaxis protocol.

A small single-centre randomised study (n = 32) by Colleoni et al,[xxxv] with a follow-up period of four weeks, although reporting no statistically significant results, demonstrated a slightly higher incidence of deep vein thrombosis (DVT) in those given a DOAC (Rivaroxaban 10 mg for 14 days) compared with aspirin(300 mg in two divided doses) (11.1% vs. 7.1%; p-value = 1). Additionally, the researchers found that wound dehiscence

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rates were higher in the DOAC group compared to the aspirin group (16.7% vs. 7.1%). Similarly, the reoperation rates and incidence of death were higher in the DOAC group (reoperation: 11.1% vs. 7.1%; p-value= 1; death: 5.6% vs. 0%; p-value = 1). Interestingly, however, there was a slightly higher rate of hospital readmission in the aspirin group compared with the DOAC group (14.3% vs. 11.1%; p-value = 1).

LIMITATIONS

The limitations of this prospective and randomized study include:
The limited number of patients, as the insufficient sample size probably influenced the degree of statistical significance with values of $p > 0.05$. The follow-up period was limited to 3 months, which may not capture all cases of late-onset VTE. The reliance on clinical symptoms to identify potential DVT cases before confirmation with USG Doppler may introduce a bias, as some cases with minimal or no symptoms might have been missed. The lack of a standardized protocol for follow-up visits may result in variability in the detection and reporting of symptoms. The study did not account for other potential confounding factors such as patient mobility status and lifestyle factors that may influence the risk of VTE.

CONCLUSION

This study compared the efficacy and safety of aspirin and rivaroxaban for venous thromboembolism (VTE) prophylaxis following total hip arthroplasty (THA) and total knee arthroplasty (TKA). Both medications demonstrated similar effectiveness in preventing VTE, with no statistically significant differences in primary outcomes, such as incidence of DVT or PE, between the two groups.

Key findings include:

Both aspirin and rivaroxaban were effective in preventing VTE after THA and TKA. There were no significant differences in the incidence of major bleeding complications between the two groups. At the end of the three-month follow-up period, five patients presented with symptoms suggestive of DVT. Subsequent USG Doppler examinations confirmed the absence of DVT in these patients, highlighting the importance of imaging for accurate diagnosis. Aspirin offers the advantage of being a cost-effective and convenient option, which could be particularly beneficial in resource-limited settings.

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