COMPARISON OF THE EFFECTIVENESS OF RIVAROXABAN VERSUS VITAMIN K ANTAGONIST IN PATIENTS WITH LOWER LIMBS DEEP VEIN THROMBOSIS

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ABSTRACT

OBJECTIVES

To compare the effectiveness of rivaroxaban and vitamin K antagonists in patients with lower limbs deep vein thrombosis.

METHODOLOGY

This quasi-experimental study was conducted in the Department of General Medicine in Khyber Teaching Hospital, Peshawar for six months with a sample size of sixty. Thirty patients were given Rivaroxaban (Group A) and the other thirty patients were given Vitamin K antagonist (Group B). In the Rivaroxaban group, patients had received 15mg twice daily for the first 3 weeks, 20 mg once daily from 3 weeks to 3 months, and followed by 10 mg once daily. In the Vitamin K antagonist group, patients had received a dose of warfarin of 2.5-5mg once daily, with a goal INR between 2-3. Patients were followed up for 3 months, every month and the effectiveness of both drugs was recorded.

RESULTS

Our study shows that in group A (Rivaroxaban), the mean age was 34 years with SD ± 10.77 and in group B (Vitamin K antagonist), the mean age was 36 years with SD ± 11.09. In Group A, 12(40%) patients were males and 18(60%) were females. In Group B, 11(37%) patients were males and 19(63%) were females. Moreover, group A was effective in 27(90%) patients while group B was effective in 25(83%).

CONCLUSION

Rivaroxaban is more effective than vitamin K antagonist in the treatment of lower limbs deep vein thrombosis.

KEYWORDS: *Vitamin K Antagonist, Rivaroxaban, Lower Limbs Deep Vein Thrombosis*

INTRODUCTION

A deep-vein thrombosis (DVT) is a clot of blood that forms within the deep veins, usually of the leg, but can occur in other veins of the body like those of the arms and the mesenteric and cerebral veins.[1] Deep-vein thrombosis is a common and important disease. It is part of the venous thromboembolism disorders which represent the third most common cause of death from cardiovascular disease after heart attacks and stroke.[2,3] Even in patients who do not get pulmonary emboli, recurrent thrombosis and "post-thrombotic syndrome" are a major cause of morbidity.[2,3] Other diseases and states can induce hypercoagulability in patients without other underlying risks for DVT. They can predispose patients to DVT, though their ability to cause DVT without intrinsic hypercoagulability is in question. The conditions include malignancy, dehydration, and use of medications (eg, estrogens). Acute hypercoagulable states also occur, as in disseminated intravascular coagulopathy (DIC) resulting from infection or heparin-induced thrombocytopenia.[4] Thromboembolism and recurrent thromboembolism appear to be serious complications of inflammatory bowel disease, with IBD patients having a threefold increased risk of thrombosis.[5] Deep-vein thrombosis and pulmonary emboli are common and often "silent" and thus go undiagnosed or are only picked up at autopsy.[6] Therefore, the incidence and prevalence are often underestimated. It is thought the annual incidence of DVT is 80 cases per 100,000, with a prevalence of lower limb DVT of 1 case per 1000 population.[7] Annually in the United States, more than 200,000 people develop venous thrombosis; of those, 50,000 cases are complicated by pulmonary embolism.[8] If there is any disruption in the balance between the coagulation and thrombolytic pathways, thrombus propagation occurs. The lower limb is the commonest site for DVT especially below the knee. It also starts preferably at low-flow sites, such as the soleal sinuses, behind venous valve pockets.[9,10] Treatment of DVT aims to prevent pulmonary embolism, reduce morbidity, and prevent or minimize the risk of developing post-thrombotic syndrome.[11] The cornerstone of treatment is anticoagulation. Treating only proximal DVT (not distal) and those with pulmonary emboli has been recommended by National Institute for Health and Care

Excellence (NICE) guidelines. In each patient, the risks of anticoagulation need to be weighed against the benefits.[12,13] Rivaroxaban's predictable pharmacologic profile and anticoagulation intensity suggest it could be associated with a reduced risk of recurrent thrombosis and/or major bleeding compared to a vitamin K antagonist in routine clinical settings. To test this hypothesis in our general population, I have planned to compare the effectiveness of rivaroxaban and vitamin K antagonists in patients with lower limbs deep vein thrombosis.

METHODOLOGY

It was a quasi-experimental study, conducted in the Department of General Medicine, Khyber Teaching Hospital, Peshawar for six months i.e., from 8/9/2021 to 8/3/2022. A total of sixty sample size was calculated with 95% confidence level and alpha =5% (two-sided) with power = 80%. Using expected effectiveness of rivaroxaban by 22.4%, as compared to 91.7%, with vitamin K antagonist in patients with lower limbs deep vein thrombosis.[14,15] n1=30 patients were in the rivaroxaban group or Group A while n2=30 patients were in the vitamin K antagonist group or Group B. Non-probability consecutive sampling technique was preferred. The inclusion criteria had patients of both genders with ages 18 to 60 years and deep vein thrombosis as per operational definition. The exclusion criteria included a history of chronic pulmonary embolism, patients who received thrombectomy or vena cava filter and patients with creatinine clearance of <30 ml/min using the Cockcroft–Gault formula. Patients with liver diseases, bacterial endocarditis, active bleeding or a high risk of bleeding, any condition that could be contraindicating anticoagulant treatment, systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg and pregnancy were also excluded carefully. Patients fulfilling the inclusion criteria from the Department of General Medicine, KTH, Peshawar were included in the study after permission from the ethical committee(Institutional Research And Ethical Review Board(IREB) Approval No.795/DME/KMC. A detailed explanation about the participation in the study was given to the patient and a written informed consent was obtained explaining the risks and benefits of the study. Randomization was conducted through block randomization, which is a method in research design used to select and divide participants into different groups to avoid selection bias and ensure that participants are assigned to groups with equal probability. Thirty patients were in the rivaroxaban group or Group A while thirty patients were in the vitamin K antagonist group or Group B. In the rivaroxaban group, patients had received 15mg twice daily for the first 3 weeks, 20 mg once daily from 3 weeks to 3 months, and followed by 10 mg once daily. In the vitamin K antagonist group, the patient had received doses of warfarin of 2.5-5mg once daily with a goal INR subsequently between 2–3. Patients were followed up every month for 3 months and effectiveness was noted as per operational definition and recorded on a designed proforma. Data was analyzed with a statistical analysis program (IBM-SPSS version 22). Frequencies and percentages were computed for qualitative variables like gender and effectiveness. Mean ±SD was presented for quantitative variables like age and weight. The chi-square test was applied to compare effectiveness in both groups taking $p \leq 0.05$ as significant. Effectiveness was stratified to age, gender and weight. Post-stratification chi-square test for both groups, $p \leq 0.05$ was considered statistically significant.

RESULTS

In this study, age distribution among two groups was analyzed as in Group A 20(67%) patients were in the age range 18-40 years, and 10(33%) patients were in the age range 41-60 years. The mean age was 34 years with SD ± 10.77. Whereas in Group B, 21(70%) patients were in the age range of 18-40 years, 9(30%) patients were in the age range of 41-60 years. The mean age was 36 years with SD ± 11.09. T Test was applied in which the P value was 0.4814. Gender distribution among the two groups was analyzed as in Group A 12(40%) patients were male and 18(60%) patients were female. Where as in Group B 11(37%) patients were male and 19(63%) patients were female. A chi-Square test was applied in which the P value was 0.7906. Weight distribution among two groups was analyzed as in Group A 22(73%) patients had a weight ≤85 Kgs and 8(27%) patients had a weight >85 Kgs. The mean weight was 80 Kg with SD ± 12.10. Where as in Group B 21(70%) patients had weight ≤85 Kg and 9(30%) patients had weight >85 Kg. The mean weight was 82 Kg with SD ± 10.22. T Test was applied in which the P value was 0.4919. Effectiveness among the two groups was analyzed as Group A (Rivaroxaban) was effective in 27(90%) patients whereas, Group B (Vitamin K antagonist) was effective in 25(83%) patients. A chi-Square test was applied in which the P value was 0.4475. (Table no I) Stratification of effectiveness to age, gender and weight is given in Tables II, III, and IV.

Table 1: Effectiveness (n=60)

Effectiveness	Group A	Group B
Effective	27(90%)	25(83%)
Not Effective	03(10%)	05(17%)
Total	30(100%)	30(100%)

Table 2: Stratification of Effectiveness w.r.t Age Distribution (n=60)

Age	Effectiveness	Group A (n=30)	Group B (n=30)	P-Value
18-40	Effective	18 (90%)	18 (86%)	
Years	Not effective	02 (10%)	03 (14%)	0.6750
Total		20 (100%)	21 (100%)	
41-60	Effective	09 (00%)	07 (00%)	
Years	Not effective	01 (00%)	02 (00%)	0.4656
Total		10 (100%)	09 (100%)	

Table 3: Stratification of Effectiveness W.R.T Gender Distribution (n=60)

Gender	Effectiveness	Group A (n=30)	Group B (n=30)	P-Value
	Effective	11 (92%)	09 (82%)	
Male	Not effective	01 (8%)	02 (18%)	0.4835
Total		12 (100%)	11 (100%)	
	Effective	16 (89%)	16 (84%)	
Female	Not effective	02 (11%)	03 (16%)	0.6773
Total		18 (100%)	19 (100%)	

Table 4: Stratification of Effectiveness w.r.t Weight Distribution

Weight	Effectiveness	Group A (n=30)	Group B (n=30)	P-Value
	Effective	20 (91%)	18 (86%)	0.5952
≤ 85 Kgs	Not effective	02 (9%)	03 (14%)	
Total		22 (100%)	21 (100%)	
	Effective	07 (88%)	07 (78%)	0.5996
>85 Kgs	Not effective	01 (12%)	02 (22%)	
Total		08 (100%)	09 (100%)	

DISCUSSION

A deep-vein thrombosis (DVT) is a clot of blood that forms within the deep veins, usually of the leg, but can occur in other veins of the body like those of the arms and the mesenteric and cerebral veins.[1] It is a common and important disease. It is part of the venous thromboembolism disorders which represent the third most common cause of death from cardiovascular disease after heart attacks and stroke.[2,3] Even in patients who do not get pulmonary emboli, recurrent thrombosis and "post-thrombotic syndrome" are a major cause of morbidity.[2,3] Our study shows that in Group A mean age was 34 years with SD ± 10.77 while in Group B mean age was 36 years with SD ± 11.09. In Group A 12(40%) patients were male and 18(60%) patients were female. Where as in Group B 11(37%) patients were male and 19(63%) patients were female. Moreover, Group A (Rivaroxaban) was effective in 27(90%) patients while Group B (Vitamin K antagonist) was effective in 25(83%) patients. Another study carried out by Houghton DE et al had reported that a total of 111 patients with DVT were studied.[16] Sixty-three rivaroxaban-treated patients were compared to 48 Vitamin K antagonist-treated patients over a median follow-up of 92 and 97 days, respectively. The percentage of patients with total or partial resolution of thrombosis was similar in rivaroxaban and Vitamin K antagonists in treated groups (95.2% vs. 91.7%, p=0.46, respectively); also the proportion of patients with total thrombus resolution was not significantly different (38.1% vs. 29.2%, p = 0.42, respectively). There was no significant difference in the proportion of patients with no thrombus resolution between rivaroxaban and Vitamin K antagonist-treated groups either (4.8% vs. 2.1%, p = 0.63). Thrombus propagation with Vitamin K antagonist in therapy was observed in 6.3% of patients treated with Vitamin K antagonist and in none of the patients from the rivaroxaban group (p=0.08). The resolution of acute lower extremity DVT in patients treated with rivaroxaban is similar to those treated with Vitamin K antagonist. Another study carried out by Farhan A et al reported that a total of 151 patients with acute symptomatic deep vein thrombosis were enrolled in the study.[17] Half of the patients were given warfarin and the other half rivaroxaban for 6 months. At three months, there were no significant differences observed in vessel patency in the rivaroxaban group (82.4%) as compared to the Vitamin K antagonist group (86.7%) but after 6 months of therapy, there was significant improvement in the patency of vessel in the rivaroxaban group. Adverse events did not show any significant differences. Rivaroxaban had an effectiveness superior to Vitamin K antagonist in terms of vessel patency after six months of therapy but adverse events were similar in both the groups. Another study carried out by Al Khateep et al reported that among 200 patients in the acute stage of deep venous thrombosis, half of them were treated by oral anti-factor Xa (rivaroxaban), which showed no significant difference in safety and effectiveness with Vitamin K antagonist.[18] Partial and complete recanalization occurred in 64 and 16%, respectively, for rivaroxaban and in 48 and 24%, for Vitamin K antagonist, whereas pulmonary embolism and bleeding occurred in 8 and 16%, respectively, for rivaroxaban and 16 and 12%, for Vitamin K antagonist. Rivaroxaban was non-inferior to Vitamin K antagonist to primary effectiveness and adverse effect outcome. One of the possible reasons for the differences in the effectiveness of Rivaroxaban and Vitamin K antagonists is the number of drug interactions Vitamin K antagonist has. Also, these patients were hospitalized and were on different medications which might have affected the effectiveness of Vitamin K antagonist. The bioavailability of Vitamin K antagonist and Rivaroxaban from oral dosing is different. Blood levels of Rivaroxaban and Vitamin K antagonist were not measured either.

LIMITATIONS

In our study, the sample size was small and was carried out at a single centre i.e., Khyber Teaching Hospital,

Peshawar. For a more reliable result that will ensure confidence, a bigger study at a multicenter, with more patients should be performed.

CONCLUSIONS

Rivaroxaban is more effective than vitamin K antagonist in the treatment of lower limbs deep vein thrombosis.

CONFLICT OF INTEREST: None

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3. ***Durkho Atif*** **-** *Drafting Manuscript; Critical Revision*
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