

## Original Research Article

# Safety and efficacy of rivaroxaban compared to standard anticoagulant therapy in the treatment of deep vein thrombosis in Indian population

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### ABSTRACT

**Background:** Pulmonary embolism (PE) is relatively a common cardiovascular complication following acute deep vein thrombosis (DVT). Around 10% of DVT patients exhibit clinical manifestations of PE. Oral drugs with adequate efficacy and safety are preferred over parenteral medications in long term prevention of PE. Our study compared rivaroxaban (factor XA inhibitor) with standard therapy (acetrom) in terms of efficacy and safety in the Indian population.

**Methods:** Patients presenting to department of general surgery at S. S. institute of medical science and research centre during the period from March 2018 to September 2020 with clinical signs and venous duplex study proven acute DVT were included in the study. Total of 64 patients were randomized into rivaroxaban group (N=28) and control group (N=36). Treatment included for rivaroxaban group was rivaroxaban (p/o) 15 mg twice daily for 21 days, followed by 20 mg once daily for 6 months. Treatment included for control group was enoxaparin (SC) overlapping with and followed by acitrom (p/o) for 6 months. The patients were looked for symptomatic recurrent PE and major or minor clinically relevant bleeding.

**Results:** Recurrent vein thrombosis noted in 1 (3.57%) patient of the rivaroxaban group and 4 (11.10%) patients in the control group. Minor bleeding seen in 3 (10.70%) patients in the rivaroxaban group and in 7 (19.40%) patients in the control group. No major bleeding was observed in rivaroxaban group and in 1 patient in the control group.

**Conclusions:** In patients with acute DVT, rivaroxaban is as efficacious as enoxaparin followed by acetram therapy, with a significantly lower rate of bleeding.

**Keywords:** Venous thromboembolism, Rivaroxaban, Vitamin K antagonist

### INTRODUCTION

Venous thromboembolism (VTE), that includes DVT and PE is relatively a common cardiovascular disorder. The incidence of VTE in general population is about one to two cases per 1000 per year.<sup>1,2</sup> VTE is the third most common cardiovascular cause of death after myocardial infarction and stroke.<sup>3,4</sup> Moreover, the risk of recurrence among survivors following VTE is around 10% per

patient during the first year after the cardiovascular event. The financial burden associated with the standard treatment and prophylaxis of VTE is considerably high.<sup>3-7</sup>

Anticoagulation is the treatment of choice for VTE.<sup>6</sup> Traditionally, standard anticoagulation therapy comprised of initial management with low molecular weight heparin (LMWH) followed by vitamin K antagonists (VKA) with/without overlapping.<sup>6-8</sup> The problems faced were

difficulty in titrating the doses of VKA to maintain the INR between 1.5 to 2.5; major and minor bleeding tendencies were high with the use of VKA; the recurrence rate of VTE was high; the patient compliance with parenteral medication was not good. However, the introduction of direct oral anticoagulants (DOACs) in the initial and long term management of VTE has solved most of the problems.<sup>9-11</sup>

In the EINSTEIN-DVT study, rivaroxaban 20 mg once daily was superior in terms of efficacy, without a significant increase in the risk of major bleeding.<sup>12,13</sup> In the EINSTEIN-PE study, rivaroxaban had shown promising efficacy, lesser risk of symptomatic recurrent VTE and much lesser risk of major bleeding.<sup>14</sup> By analyzing both the studies, rivaroxaban had similar efficacy and lesser risk of major bleeding on comparing with the standard therapy.

Rivaroxaban is a once daily direct factor XA inhibitor indicated in the initial and long term management of VTE.<sup>15</sup> It has a very good oral bioavailability ( $\geq 80\%$ ) and more predictable pharmacokinetics and pharmacodynamics.<sup>16-18</sup> These characteristics provide the basis for use of this drug without the need for regular coagulation monitoring. The onset of action of rivaroxaban has been shown to be as fast as that of LMWH enoxaparin.<sup>19</sup> The peak plasma concentrations are achieved within 2-4 hours of oral administration and has a mean half-life of approximately 9 hours and gets excreted through urine and faeces.<sup>17,18</sup> Rivaroxaban has negligible drug-drug or drug-food interactions.<sup>20-23</sup> However, rivaroxaban should better be taken with food to attain and maintain high oral bioavailability.<sup>23</sup>

### **Aims and objectives**

The aims and objectives of this study were to study the efficacy of rivaroxaban, in terms of symptomatic recurrent VTE, in the Indian population compared with standard therapy in the management of VTE and to study the safety profile of rivaroxaban, in terms of major or minor clinically relevant bleeding, in the Indian population compared with standard therapy in the management of VTE.

## **METHODS**

This is a tertiary care hospital based prospective clinical study conducted in the department of general surgery at S. S. institute of medical sciences and research centre, Davangere from March 2018 to September 2020.

### **Inclusion criteria**

Patients presenting to department of general surgery at S. S. institute of medical sciences and research centre with clinical features and radiological findings of DVT of lower limb and patients with age group of 20 years up to 85 years were included in the study.

### **Exclusion criteria**

Patients with DVT secondary to malignancy and pregnancy, extensive DVT involving inferior vena cava (IVC), DVT patients already having symptoms of PE at emergency department, patients age less than 20 years and above 85 years were excluded from the study.

### **Method**

All the patients underwent complete clinical evaluation and venous duplex studies. Total of 64 patients were randomized into rivaroxaban group (N=28) and control group (N=36). Patients in rivaroxaban group were treated with tablet rivaroxaban (p/o) 15 mg twice daily for 21 days, followed by 20 mg once daily for 6 months. In control group the patients were treated with the standard therapy of injection enoxaparin (0.6 mg, subcutaneous) initially overlapping with and followed by tablet acitrom (2 mg per oral) for 6 months. Patients in both the groups were provided complete bed rest and were hospitalized for minimum of 7 days. The dose of tablet acetrom was titrated as per needs in control group to maintain INR between 1.5 to 2.5. All the patients were subjected to venous duplex scan again at the time of discharge as per standard protocol.

Patients were made aware of the complications like shortness of breath, difficulty in breathing, minor bleeding like gum and nasal bleeding, major bleeding like blood vomiting and blood in urine and stools. Patients were informed to immediately stop the medications and come to surgery OPD/emergency department if they exhibit above mentioned symptoms. Patients coming back with complications were subjected to CT thorax/coagulation profile and were managed accordingly.

The usual follow up period comprised of weekly once in the first month followed by monthly once for the next 5 months. During the follow up, patients symptoms if any, were noted down and acted accordingly.

### **Statistical analysis**

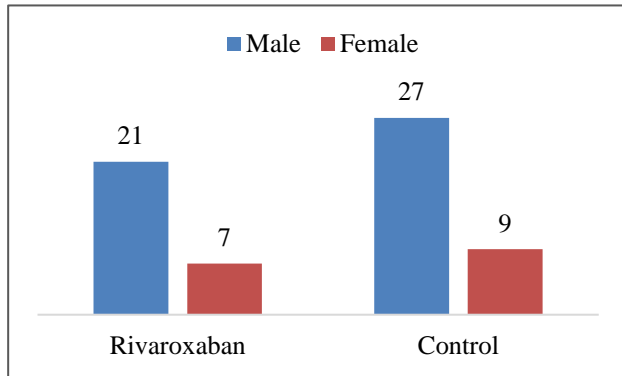
Mean and Fisher exact test were used for the statistical analysis in this study.

## **RESULTS**

A total of 80 patients were included, of which later 16 patients were excluded as 8 patients were found to have malignancy, 4 patients were pregnant and 4 patients had extensive DVT till IVC. The final study group consisted of 64 patients, 28 of which were included in rivaroxaban group and 36 were included in control group.

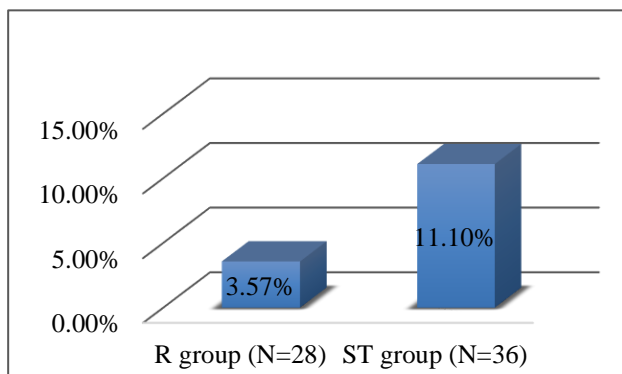
The mean age of the patients in the rivaroxaban group was 54.3 years and in the control group it was 56.1 years.

The difference in mean age between the two groups was not statistically significant (Figure 1).

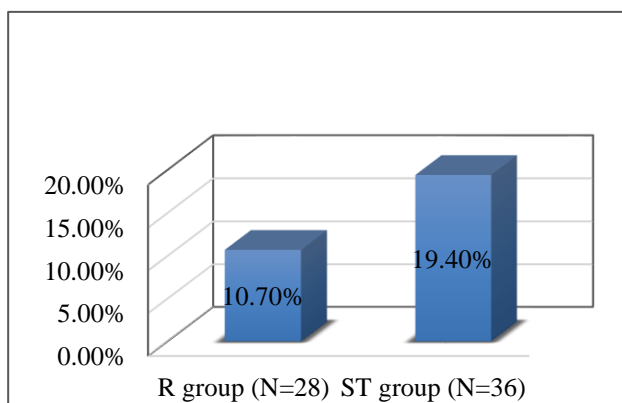


**Figure 1: Gender distribution.**

In the rivaroxaban group, 1 patient (3.57%) developed recurrent VTE at 3rd month of follow up. In the control group 4 patients (11.1%) developed recurrent VTE at 3rd and 4th month of follow up (Fisher exact=0.37,  $p<0.05$ ). No patients developed PE in both the groups in the complete 6 months follow up (Figure 2).



**Figure 2: Efficacy outcome (recurrent VTE) in both the groups.**



**Figure 3: Safety outcome (bleeding) in both the groups.**

Minor bleeding like gum bleeding and nasal bleeding were noted in 3 patients (10.7%) in rivaroxaban group

and in 7 patients (19.4%) in control group (Fisher exact=0.49,  $p<0.05$ ). No major bleedings were noted in rivaroxaban group and 1 patient (2.78%) developed blood in urine in control group (Fisher exact=1,  $p<0.05$ ) (Figure 3).

## DISCUSSION

Efficacy and safety of rivaroxaban have been well proven in the EINSTEIN DVT, EINSTEIN PE, XALIA and REMOTEV studies, but consensus is still unclear in Indian population. In our study, after a mean follow up of 180 days, no mortality was seen in either of the group. In XALIA (factor Xa inhibition with rivaroxaban for long-term and initial anticoagulation in DVT), a multicenter, prospective, noninterventional and observational study the all-cause mortality frequency was 0.4% (11/2505) in the rivaroxaban group and 3.4% (69/2010) in the standard anticoagulation group (propensity score-adjusted HR 0.51; 95% CI 0.24-1.07;  $p=0.074$ ). In the REMOTEV study after the propensity score-adjusted samples, major and clinically relevant non-major bleeding (HR 0.37; 95% CI 0.15 to 0.93,  $p<0.05$ ), all cause death (HR 0.21 [95% CI, 0.06 to 0.66;  $p<0.01$ ) and the composite of recurrent VTE, major and clinically relevant non-major bleeding and all-cause mortality (HR 0.35; 95% CI 0.17 to 0.71;  $p<0.01$ ) were significantly lower in the rivaroxaban group compared to the VKA group. Zero mortality in our study might either be because our study excluded elderly and cancer patients, or because of small study group and mean follow up of only 180 days.

In the rivaroxaban group in our study, 1 patient (3.57%) developed recurrent VTE at 3rd month of follow up and 4 patients (11.1%) in the control group developed recurrent VTE at 3rd and 4th month of follow up. In XALIA, the frequency of recurrent venous thromboembolism was 1.4% (36/2505) in the rivaroxaban group and 2.3% (47/2010) in the standard anticoagulation group (propensity score-adjusted HR 0.91; 95% CI 0.54-1.54;  $p=0.72$ ). In REMOTEV the recurrent VTE rate was 1.4% (4/280) in the rivaroxaban group, 3.1% (3/96) in the VKA group and 11.6% (8/69) in the heparin/fondaparinux group. In EINSTEIN DVT, the primary efficacy outcome (recurrent VTE) occurred in 2.1% of patients in the rivaroxaban group and in 3.0% of patients in the standard therapy group (HR 0.68; 95% CI 0.44 to 1.04;  $p<0.001$  for noninferiority with one sided test and  $p=0.08$  for superiority with a two sided test). By day 21 (the end of twice daily rivaroxaban dosing), the primary efficacy outcome (recurrent VTE) had occurred in 21 patients (1.2%) in the rivaroxaban group and in 29 patients (1.7%) in the standard therapy group. In addition, it has been shown that in routine practice, VTE patients who continue rivaroxaban therapy after the initial 3 or 6 month treatment period have a significantly lower risk for VTE recurrence without significant increased risk for major bleeding.<sup>23</sup> The rate of VTE is slightly increased in our rivaroxaban group as compared with other studies.

This might be as a result of small study group as compared with other studies.

Minor bleeding like gum bleeding and nasal bleeding were noted in 3 patients (10.7%) in rivaroxaban group and in 7 patients (19.4%) in control group. No major bleedings were noted in rivaroxaban group and 1 patient (2.78%) developed blood in urine in control group which might be considered as major bleeding. In EINSTEIN DVT study the principal safety outcome first major or clinically relevant nonmajor bleeding- occurred in 139 patients (8.1%) given rivaroxaban and in 138 patients (8.1%) given standard therapy (HR with rivaroxaban 0.97; 95% CI 0.76 to 1.22;  $p=0.77$ ). In REMOTEV study, the major and clinically relevant bleeding rate was 5.4% (15/280) in the rivaroxaban group, 9.4% (9/96) in the VKA group and 7.2% (5/69) in the heparin/fondaparinux group. In XALIA study, the frequency of major bleeding was 0.8% (19/2505) in the rivaroxaban group and 2.1% (43/2010) in the standard anticoagulation group, with a propensity score adjusted hazard ratio (HR) of 0.77 (95% CI 0.40-1.50;  $p=0.44$ ). Marginally high bleeding frequency in our study can be attributed to small study group than compared with the other studies.

Our study had certain limitations and bias. Firstly, the categorization of the patients into study and control groups was not equal because of difficulty in randomization. Secondly, the total number of patients included in the study was less due to strict exclusion criteria. Thirdly, our study was conducted in a single centre, bias at various levels were inevitable. Many such observational/interventional, multicentre (including various geographical variables) studies including the patients with the extremes of ages, required to come to a consensus.

## CONCLUSION

Our study concludes that rivaroxaban can be a safe and efficient choice for the initial and long term anticoagulation in the treatment of VTE. But it requires further more large group studies with long term follow up to consider rivaroxaban as the drug of choice for VTE anticoagulation. Furthermore, its safety in older age, cancer patients and pregnancy needs to be studied in detail.

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