Section: Orthopaedics

Original Research Article

COMPARISON OF EFFICACY AND SAFETY OF RIVAROXABAN VS. ASPIRIN FOR VENOUS THROMBOEMBOLISM PROPHYLAXIS FOLLOWING MAJOR ORTHOPAEDIC SURGERIES- A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: To compare the efficacy and safety of newer approved oral anticoagulant rivaroxaban with conventionally used aspirin in prevention of Venous Thromboembolism (VTE) following major orthopedic surgeries.

Material and Methods: 50 patients who were operated for spine, pelvis and lower limb surgeries were randomized into two groups A and B. Group A received 150 mg of acetylsalicylic acid (Aspirin) and Group B received 10 mg of Rivaroxaban daily for a period of 35 days. Follow up was performed at 2, 4 and 6 weeks and evaluated clinically, radiologically (Venous Doppler study) and with necessary investigations. Outcomes of interest included, incidence of deep vein thrombosis, pulmonary thromboembolism, incidence of major bleeding, clinically relevant bleeding, minor bleeding, and wound complications like hematoma, infections and myocardial infarction, stroke, readmissions, re-operations and mortality.

Results: There were no significant differences between two groups with respect to any outcome measures like deep vein thrombosis (DVT), pulmonary thromboembolism, local complications, systemic complications, bleeding, readmission to hospital, reoperation, or death ($p > 0.05$) between groups.

Conclusion: Aspirin was found to be equally efficient and safe when compared to Rivaroxaban in chemoprophylaxis of Venous Thromboembolism (VTE) following major orthopedic surgeries.

Keywords: Venous Thromboembolism (VTE), Rivaroxaban, Aspirin.

INTRODUCTION

Venous thromboembolism (VTE) is a serious complication with a high incidence during and after hospitalization, and it is also an important factor in perioperative mortality and unexpected deaths in hospitals.[2] When preventive measures are not used, the incidence of DVT may reach 60% in the 90 days after surgery, and the incidence of fatal pulmonary embolism may reach up to 1.5%.[2] The ratio of asymptomatic DVT at hospital discharge to symptomatic VTE within next three months is about 5:1 following THR.[2] There is general agreement that prophylaxis against venous thromboembolism (VTE) is necessary, but the ideal prophylactic regimen has not been identified.[5] Orthopaedic surgeons are particularly concerned about postoperative bleeding because it may be associated with hematoma, infection, and reoperation, all of which can have a negative impact on outcomes.[5] Current prophylaxis agents include vitamin K antagonists (warfarin), low- molecular weight heparins (enoxaparin, dalteparin, fondaparinux), oral factor-Xa inhibitors (rivaroxaban, apixaban), direct thrombin inhibitors (dabigatran), and aspirin. There has been extensive study of each of these prophylactic modalities.

However, there continues to be substantial debate with regard to the optimal pharmacological

modality.[6] The selection of a prophylactic regimen is a balance between efficacy and safety.[8]

Rivaroxaban

It is an oral Factor Xa inhibitor. Route of administration is oral. With regard to pharmacokinetics, the biological half-life is 5 to 9 hours (11to 13 hours in elderly patients), and it is primarily metabolized through the liver and is primarily eliminated through the renal system. The reversal agents are and Exanet alfa and prothrombin concentrate complex. Contraindications are liver disease (Child-Pugh class B or C) and kidney disease (creatinine clearance, 30mL/min or Serum creatinine >2.5mg/dl). It has predictable stable pharmacokinetics and does not require dose adjustment for age, sex, body, weight, or race, which abrogates the need for outpatient monitoring.[6] Aspirin

Acetylsalicylic acid or aspirin exerts its effects by irreversibly acetylating a serine residue in the active site of the cyclooxygenase enzyme, decreasing formation of potent platelet aggregators. The route is oral, and dosing is variable. With regard to pharmacokinetics, the biological half-life is 2 to 4.5 hours. The reversal agent is platelets. A notable contraindication is hypersensitivity to non-steroidal anti- inflammatory drugs (NSAIDs). It does not require outpatient monitoring.[6]

Aspirin is an inexpensive, generic, and widely available anti-platelet drug. Clinical trials and meta-analyses have suggested that aspirin may be effective for the prevention of venous thromboembolism postoperatively, but comparisons with direct oral anticoagulants are lacking.[11]

Aim of the study

To compare the newer approved oral anticoagulant rivaroxaban with conventionally used aspirin in prevention of venous thromboembolism (VTE) following major orthopedic surgeries.

Purpose of this study

To compare the efficacy, safety of rivaroxaban with aspirin in prevention of venous thromboembolism and to study the complications associated with administration of aspirin and rivaroxaban.

MATERIALS AND METHODS

Source of data: Post-operative patients satisfying inclusion criteria admitted in Department of Orthopaedics in Basaveshwara medical college hospital & research Centre during the period of August 2023 to October 2023 were included in the study.

Study design: Randomized control study

Study period: 3 Months (August 2023 to October 2023)

Place of study: Orthopaedic department at Basaveshwara Medical College Hospital, Chitradurga

Sample size: 50 (Convenience sampling)

After going through medical research department section in Basaveshwara medical college and research hospital, the average number of patients operated was around 430 in the year 2022. So considering the similar conditions, any patient who have fulfilled the inclusion criteria were included in the study in a study period of 3 months.

Sampling technique - Convenience sampling meeting the inclusion criteria

Inclusion Criteria

Patient above 21 yrs of age

Patient undergoing major surgeries (spine, pelvis and lower limb) including trauma and arthroplasty surgeries

Patient willing to give informed consent

Exclusion Criteria

Patients allergic to one of the medications Patients with coagulation disorders

Patients on chronic anticoagulation other than anti platelet medications Patients with liver disease

Patients with past history of haemorrhages in past 3 months (Gastrointestinal bleed, cerebraland other haemorrhages)

Patients with past history of DVT or Pulmonary Thromboembolism Patient with recent malignancy.

Methodology

After obtaining approval and clearance from the institutional ethics committee, the patients fulfilling the inclusion criteria were enrolled for the study after obtaining informed consent. Patients who met the eligibility criteria have been included in this study. A thorough history was taken and clinical examination was done.

Doppler venous study lower limbs were done at 2, 4 and 6 weeks post operatively and at anytime if the patient shows signs and symptoms of DVT. CT pulmonary angiogram was done in suspected cases of pulmonary embolism.

Patients were randomized to either aspirin group or rivaroxaban group according to the computer generated random number table.

Group A – Aspirin group Group B – Rivaroxaban group.

A total of 50 patients (Group A, n=25; Group B, n=25) were included in the final analysis after inclusion and exclusion criteria were applied. A two-sided p-value of

≤ 0.05 was set as statistically significant. For comparisons between the study groups, we used Student t-test for continuous variables and Chi square test and Fisher exact test (If cells had count less than 5) for discrete variables, according to the data type.

Procedure

Preoperatively all necessary investigations were done like complete blood count, liver function tests, renal function tests and coagulation profile. On the post-operative day 1 of surgery, anticoagulants were started. Oral Aspirin 150 mg once a day for group A and Oral Rivaroxaban 10 mg once a day for group B. These anticoagulants were continued for 35 days

(5 weeks) postoperatively (Table 1). Patients were followed up for a period of 6 weeks.

Demographic data

Among 50 participants, who underwent trial, mean age was found to be 54.08 ± 17.99 in Group A and 51.68 ± 17.28 in Group B. 33 participants were male and 17 were female (Fig.1). Group A consisted of 16 males (64%) and 9 females (36%). Group B consisted of 17 males (68%) and 8 females (32%). All 50 participants who were enrolled underwent orthopaedic surgery. Among them 28 underwent surgeries for lower limb fractures (56%), 10 underwent spine surgeries (20%), 4 underwent surgery for trauma to pelvis (8%) and 8 underwent arthroplasty surgery (16%) (Fig.2 and Fig.3).

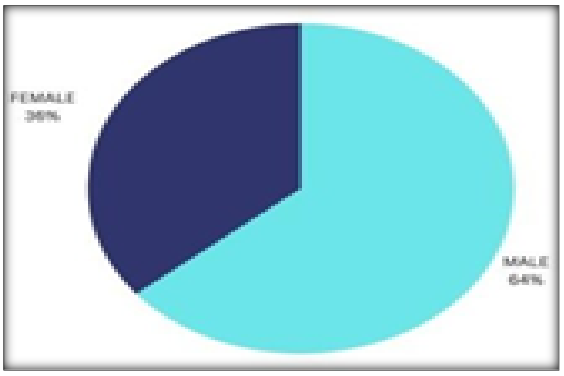

Figure 1

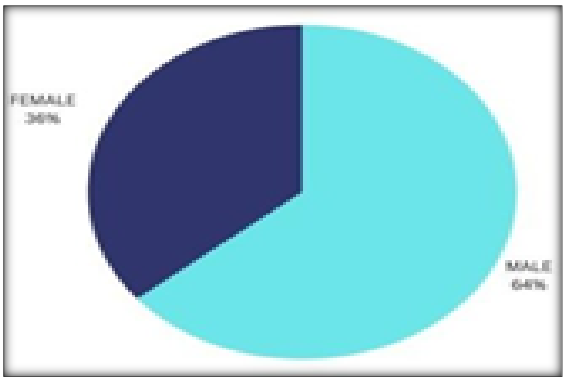

Figure 2

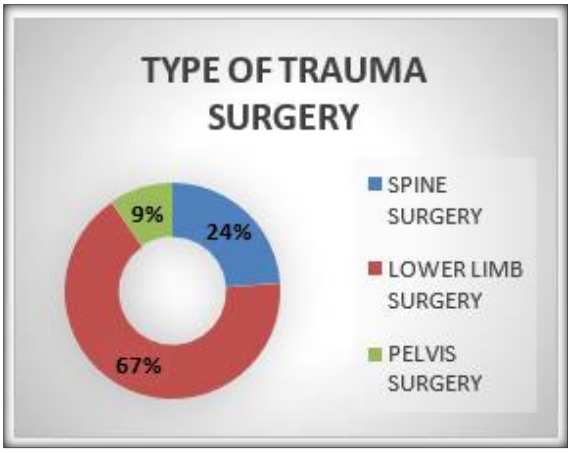

Figure 3

Among our participants, 7 were obese (BMI ≥30). Four in Group A (aspirin group) and three in Group B (Rivaroxaban group). Co morbidities of both Group A and Group B has been summarised in Table 2. There weren't any significant differences in co morbidities with respect to both aspirin and rivaroxaban groups. There were 8 diabetic individuals, three in Group A and 5 in Group B. There were 11 hypertensive participants, five in Group A and six in Group B. Among our participants of study, 7 had COPD, four in Group A and three in Group B. And 2 patients had neurological disorders (Alzheimer's disease), one in each group. 5 patients had chronic kidney disease, three in group and two in Group B. Totally 5 female patients had hypothyroidism, three in Group A and two in Group B.

Follow Up and Criteria for Evaluation

The patients were followed up at 2 weeks, 4 weeks, 6 weeks. Clinically for signs and symptoms of DVT. Radiologically with Doppler venous study lower limbs at 2, 4 and 6 weeks regularly and symptomatic DVT cases anytime and CT pulmonary angiogram was done in suspected cases of pulmonary embolism. Hematological investigations like Complete blood count, Bleeding time, clotting time, PT INR, APTT, liver function tests, renal function tests were done if necessary in the follow- up period.

Outcome evaluation

The primary outcome efficacies of the drugs were evaluated based on the incidence of Venous Thromboembolism/Deep vein thrombosis and pulmonary embolism.

DVT was diagnosed clinically according to the criteria of Fraser et al.[20]

A score of 3 or higher indicates a high probability of deep vein thrombosis; 1 or 2, a moderate probability: and 0 or lower, a low probability. In patients with symptoms in both legs, the more symptomatic leg was used.

Secondary outcome (safety) was evaluated by the incidence of bleeding events (bleeding at the surgical wound or anywhere in the body), including major, clinically relevant bleeding, and minor bleeding according to Anderson's criteria13.

Major bleeding: The primary safety end point was bleeding, which was described as major if it was overt and fulfilled at least one of the following criteria: fatal bleeding, symptomatic bleeding into a critical area or organ, or bleeding that caused a 20g/L decrease or more in hemoglobin level or led to transfusion of two or more units of whole blood or red blood cells.

Clinically relevant bleeding: It is defined as clinically relevant but non-major if it resulted in hospitalization, reoperation, aspiration, or a wound hematoma complicated by infection.

Minor bleeding: It is defined as overt bleeding that did not fall into one of the aforementioned categories.[12]

Secondary outcomes (Safety) / Post-operative complications were evaluated by the incidence of wound complications – hematoma, infections (surgical site infections), myocardial infarction, stroke, readmissions, re-operations and mortality.

Statistical Analysis

The data obtained will be entered into Microsoft excel spread sheet, and then it was transferred and analyzed using appropriate statistical software. Appropriate Parametric and non-parametric tests were used according to the distribution of data. P value of 0.05 was considered significant. A two-sided p-value of ≤0.05 was set as statistically significant. For comparisons between the study groups, we used Student t-test for continuous variables and Chi square test and Fisher exact test (If cells had count less than 5) for discrete variables, according to the data type.

Table 1: Prophylaxis Protocol

Parameters	Group A (Aspirin group) n=25	Group B (Rivaroxaban group) n=25
Number of patients receiving drugs	25	25
Drugs started on	Post op day 1	Post op day 1
Duration of prophylaxis	35 days post-surgery	35 days post-surgery
Follow up duration	6 weeks	6 weeks

Table 2: Basic characteristics of participants of both groups

Parameters	Group A (Aspirin group) n=25	Group B (Rivaroxaban group) n=25	P-value
Age (in years) mean ±SD	54.08 ±17.28	51.68± 17.99	0.633, NS
Gender			
Male	16 (64%)	17 (68%)	0.765, NS
Female	9 (36%)	8 (32%)	
Body mass index			
BMI≥30	4 (16%)	3 (12%)	0.684, NS
BMI<30	21(84%)	22 (88%)	
Surgical procedure			
Arthroplasty	***5 (20%)***	***3 (12%)***	0.44, NS
Trauma	***20 (80%)***	***22 (88%)***	
Lower limb	15 (75%)	13 (59.1%)	0.484, NS
Pelvis	4 (20%)	6 (27.27%)	
Spine	1 (5%)	3 (13.63%)	
Co morbidities			
Diabetes mellitus	3 (12%)	5(20%)	0.98, NS
Hypertension	5 (20%)	6 (24%)	
COPD	4 (16%)	3 (12%)	
Neurological disorders	1 (4%)	1 (4%)	
Chronic kidney disease	3 (12%)	2 (8%)	
Thyroid disorders	3 (12%)	2 (8%)	
Nil	6 (24%)	6 (24%)	

*NS- Not significant

Table 3: Clinical evaluation table

Clinical characteristics	Score
Active cancer (treatment ongoing, within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden > 3 d or major surgery within 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis at least as likely as deep vein thrombosis	-2

RESULTS

Our selected sample consisted of 50 patients; 33 males (66%) and 17 females (34%). Patients were divided into 2 groups, group A and group B. Group A consisted of 16 males and 9 females. Group B consisted of 17 males and 8 females. Basic parameters of participants were shown in Table 4. There were no significant differences found between two groups in terms of age, sex, pre-operative haemoglobin, Coagulation profile. There were no significant differences found in liver and renal function test of both groups pre operatively. [Table 4]

Primary outcome - Efficacy

In our study, a total of 3 cases of venous thromboembolism were reported. 2 in Group A and 1 in Group B. Among 2 cases reported in Group A, one was reported at 2 weeks and other at 6 weeks follow up. And 1 case of VTE in Group B was reported at 2 weeks follow-up. No cases of pulmonary thromboembolism were reported in both

groups based on our study as shown in Table 5. There was no statistical difference in term of primary outcomes between two groups of study. [Table 5]

Secondary outcomes - Safety:

Among the participants of our study, 2 participants developed minor bleeding complications, one in each group. One patient from Group B developed clinically relevant bleeding, who developed hematoma followed by infection at the surgical site, was re admitted and underwent re-operation (wound debridement) was done. None of our participants had stroke or myocardial infarction. There were no reported deaths among our participants. [Table 6] With respect to safety outcomes (post-operative complications), there were no difference statistically between aspirin and rivaroxaban groups

Table 4: Pre-operative Haematological investigations of both groups

Parameters	Group A (Aspirin group) n=25 Mean ±SD	Group B (Rivaroxaban group) n=25 Mean ±SD	P-value
Haemoglobin	12.792±2.065	13.048±2.298	0.676, NS
Total leucocyte count	11287.6±2330.839	10969.2±1857.7	0.596, NS
Platelet count	3.30±0.72	3.315±1.029	0.953, NS
Coagulation profile			
Bleeding time	288.72±65.57	284.16±42.394	0.772, NS
Clotting time	666.4±98.06	682.4±88.142	0.547, NS
Prothrombin time	14.244±1.881	14.592±1.624	0.487, NS
INR	1.012±0.136	0.98±0.0645	0.293, NS
APTT	28.032±4.04	28.992±3.471	0.372, NS
Liver function test			
Total bilirubin	0.9884±0.156	1.012±0.209	0.653, NS
SGOT	24.28±7.294	25.76±6.869	0.464, NS
SGPT	23.44±6.265	24.48±6.659	0.572, NS
Renal function tests			
Serum Creatinine	1.076±0.332	0.976±0.341	0.299, NS
Blood urea	37.6±20.734	29.64±18.34	0.157, NS

***NS- Not significant**

Table 5: Efficacy of drugs - Rates of VTE and PE between two groups

Events	2 weeks	4 weeks	6 weeks	Anytime	Total	P-value
VTE (DVT)						
Aspirin group	1	Nil	1	Nil	2	0.55, NS
Rivaroxaban group	1	Nil	Nil	Nil	1	
Pulmonary embolism						
Aspirin group	Nil	Nil	Nil	Nil	Nil	1, NS
Rivaroxaban group	Nil	Nil	Nil	Nil	Nil	

***NS- Not significant**

Table 6: Safety outcomes- Post operative complications

Parameters	Group A(Aspirin group) n=25	Group B (Rivaroxaban group) n=25	P- value
Bleeding			
Major	Nil	Nil	0.796, NS
Clinically relevant	Nil	1	
Minor	1	1	
Wound complications			
Hematoma	Nil	1	0.353, NS
Infections – Surgical site	Nil	1	
Stroke	Nil	Nil	1, NS
Myocardial infarction	Nil	Nil	1, NS
Re admission	Nil	1	0.313, NS
Re operation	Nil	1	0.313, NS
Mortality	Nil	Nil	1, NS

***NS- Not significant**

DISCUSSION

Venous thromboembolism (VTE) is an important cause of readmissions or mortality following major orthopaedic surgeries. Chemoprophylaxis is one prong of this strategy, along with multidisciplinary care and early mobilization. There has been substantial debate regarding the preferred chemical prophylactic agent among aspirin, enoxaparin, warfarin, and factor Xa inhibitors when weighing VTE prophylaxis efficacy versus bleeding risk3. However, there is no published systematic review and meta-analysis comparing the outcomes of aspirin and rivaroxaban9. In our study we compared

conventionally used aspirin with newly approved oral anticoagulant rivaroxaban.Our results showed that there were no significant differences between aspirin and rivaroxaban in terms of efficacy and complications. Aspirin thromboprophylaxis may offer a cost-effective alternative to practitioners who may fear non-adherence to therapy in their patients due to financial difficulties.[4]

In a systematic review done by Soheir S. Adam, Jennifer R. McDuffie et al. where they compared the effectiveness of new oral anticoagulants and standard thromboprophylaxis in patients having total hip or knee replacement. Their review showed that new oral anticoagulants are as effective as standard thromboprophylaxis for thromboprophylaxis after THR and TKR.[14]

Qiang Huang, Shu-xing Xing, et al. did a retrospective study comparing efficacy and safety of aspirin and rivaroxaban following Enoxaparin Treatment for Prevention of VTE after hip fracture surgery. Their results showed that extended prophylaxis for 21 days with aspirin was equivalent to the direct oral anticoagulant rivaroxaban after hip fracture surgery with an initial 5-day postoperative course of enoxaparin. They concluded that Aspirin may be an effective, safe, convenient, and cheap alternative for extended prophylaxis after hip fracture surgery.[4] Their study correlates well with our study.

Similar to our results, in a Meta analysis study done by Joshua Xu, Aran Kanagaratnam et al. where they compared aspirin against rivaroxaban for VTE prophylaxis after hip and knee arthroplasty showed that aspirin was not significantly different to rivaroxaban for prevention of VTE or adverse events after TKA or THA.[9]

In a prospective study conducted by Jose LuizColleoni, Fernando Noel Ribeiro et al, where they studied 32 patients with osteoarthritis undergoing TKA, compared aspirin against rivaroxaban for VTE prophylaxis, which showed that there were no identifiable differences in local complications, systemic complications, deep vein thrombosis (DVT), and readmission tohospital, reoperation, or death between rivaroxaban and aspirin. And they concluded that both aspirin and rivaroxaban can be considered for VTE prevention after TKA1.

In a Randomized control trial done by D.R. Anderson, M. Dunbar, J et al., on 3424 patients (1804 undergoing total hip arthroplasty and 1620 undergoingtotal knee arthroplasty), where they compared aspirin and rivaroxaban for VTE prophylaxis concluded that patients who received extended prophylaxis with aspirin was not significantly different from rivaroxaban in the prevention of symptomatic venous thromboembolism.[11]

Our study results have shown that there were no identifiable differences in local and systemic complications, readmissions or mortality between aspirin and rivaroxaban groups.

Guoping Le, Chengzhi Yang, et al. did a meta-analysis where they compared the efficacy and safety of aspirin and rivaroxaban for venous thromboembolism prophylaxis after total hip or knee arthroplasty. Their study inferred that aspirin and rivaroxaban offered similar effect in the prevention of VTE after total knee arthroplasty or total hip arthroplasty. However, rivaroxaban seemed to have better effect than aspirin in reducing the risk of DVT, and aspirin was safer than rivaroxaban in decreasing the blood transfusion rate.[10]

V Loganathan, A Hua et al did a retrospective cohort study on 479 patients undergoing hip or knee arthroplasty, where they administered enoxaparin in the inpatient setting, followed by rivaroxaban upon hospital discharge and studied the efficacy and safety of rivaroxaban thromboprophylaxis. Their study showed that Rivaroxaban is an effective and safe anticoagulant for thromboprophylaxis after hip arthroplasty or knee arthroplasty if used in a modified regimen involving enoxaparin administered in the inpatient setting followed by rivaroxaban upon hospital discharge.[16]

JianXie, Mingyang Jiang et al. did a Meta-Analysis of 9 Randomized Controlled Trials comprising 7,656 patients who underwent TKA or THA, where they compared Rivaroxaban and Aspirin in Prevention of Venous Thromboembolism. In contrary to our study results, their study indicated that rivaroxaban can significantly reduce the incidence of VTE when compared with aspirin. The preventive effect of rivaroxaban on VTE was more potent than that of aspirin. However, similar to our results, rivaroxaban had some negative side effects to patients such as non-major bleeding compared to aspirin.[18]

In a Meta-analysis done by Abiram Bala MD, James I. Huddleston et al. they compared aspirin. warfarin, enoxaparin or factor Xa inhibitors for VTE prophylaxis after TKA. Their analysis showed that factor Xa inhibitors provided improved VTE prophylaxis compared with enoxaparin and warfarin, with a lower rate of blood transfusion. Aspirin provided comparable VTE prophylaxis compared with factor Xa inhibitors with improved VTE prophylaxis compared with enoxaparin and warfarin with the lowest risk of bleeding.[3]

The choice of thromboprophylaxis after major orthopaedic surgeries remains an important issue. Our study showed that aspirin is as effective as newer oral anticoagulant rivaroxaban with a favourable complication profile. But aspirin being cost effectivemay benefit more than rivaroxaban.

CONCLUSION

Aspirin was found to be equally efficient and safe when compared to Rivaroxaban in chemoprophylaxis of Venous Thromboembolism (VTE) following major orthopaedic surgeries. Aspirin has the advantage of being cost effective and easily available There were no significant

differences in efficacy and safety between aspirin and rivaroxaban.

Hence aspirin can be preferred over rivoraxaban in chemoprophylaxis of Venous Thromboembolism.

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