Efficacy of Rivaroxaban in Prophylaxis against Venous Thromboembolism after Total Knee Arthroplasty

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ABSTRACT

BACKGROUND

Venous thromboembolism is a potentially fatal complication after major orthopaedic surgeries like total knee arthroplasty, and total hip arthroplasty. Venous thromboembolism comprises of deep vein thrombosis, pulmonary embolism. It is a preventable complication of in-hospital mortality. The prophylaxis to prevent VTE varies from warfarin, low molecular weight heparin like enoxaparin, Fondaparinux sodium, direct factor Xa inhibitor like rivaroxaban and apixaban, and mechanical thromboprophylaxis.

METHODS

We studied the efficacy of oral rivaroxaban 10 mg once daily for 14 days in the prevention of VTE in 60 elective cases of total knee arthroplasty. The study was done from August 2018 to December 2019. All the operated cases were cemented with cruciate retaining prosthesis with mean operative time of 120 minutes without any intra-op events. Oral Rivaroxaban 10 mg was given after 6-8 hours after wound closure and continued for 14 days. All the patients were closely monitored for signs and symptoms of DVT, PE with Wells DVT score followed by venous angiogram and signs of pulmonary embolism were evaluated with modified Gurd and Wilson criteria and subsequent CT pulmonary angiogram.

RESULTS

One patient developed deep venous thromboembolism (1.6%). No bleeding manifestations or pulmonary embolism were reported. In the study, majority of the subjects were in the age group of <60 years (46.7%); 70% were females and 30% were males; 48.3% were overweight; 33.3% were obese grade I and 3.3% were obese grade II.

CONCLUSIONS

Once daily oral dose of rivaroxaban 10 mg for 14 days is an effective modality in reducing the number of cases of VTE after Total knee arthroplasty. Our study highlights the potential benefits and risk associated with the use of rivaroxaban as the drug of choice for thromboprophylaxis. The ease of administration of oral agents compared to subcutaneously given agents like Enoxaparin will lead to better patient compliance and early discharge from hospital.

KEYWORDS

Venous Thromboembolism, Total Knee Arthroplasty, Rivaroxaban, Deep Vein Thrombosis, Pulmonary Embolism

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DOI: 10.18410/jebmh/2020/319

How to Cite This Article:
Kalyanasundaram S, Khalid MF, Raghavendra S, et al. Efficacy of rivaroxaban in prophylaxis against venous thromboembolism after total knee arthroplasty. J. Evid. Based Med. Healthc. 2020; 7(31), 1517-1520. DOI: 10.18410/jebmh/2020/319

Submission 28-05-2020,
Peer Review 31-05-2020,
Acceptance 17-06-2020,
Published 30-07-2020.

BACKGROUND

Venous thromboembolism is not uncommon and is a potential complication after major orthopaedic surgeries like Total knee Arthroplasty, and Total Hip Arthroplasty. Venous thromboembolism comprises of Deep vein thrombosis, pulmonary embolism.[1,2] The overall rate of fatal pulmonary embolism is 0.059%.[3] The incidence of fatal PE varies from 0.0059% to 0.43%.[3-6] It is a preventable complication of in-hospital mortality. The prophylaxis to prevent VTE varies from warfarin, low molecular weight heparin like enoxaparin, Fondaparinux sodium, direct factor Xa inhibitor like rivaroxaban and apixaban, mechanical thromboprophylaxis.

In our study we reviewed the efficacy of Rivaroxaban- an oral oxazolidinone based anticoagulant, is a potent, selective direct inhibitor of factor Xa that is used in the prevention of venous thromboembolism (VTE) in adult patients after total hip or knee replacement surgery. Orally 10 mg tablet once daily for 14 days in preventing VTE after Total knee arthroplasty.[7]

Pharmacological Properties

Rivaroxaban is a potent oral direct inhibitor of serine endopeptidase factor Xa and inhibits both free Xa and fXa bound in the prothrombinase complex. Factor Xa, an enzyme of the coagulation cascade involved in the formation of thrombin. The potency of fXa inhibition occurs primarily as a result of rivaroxaban binding with high selectivity to the S1 and S4 pockets of the serine end peptidase.[8] Rivaroxaban classified as low clearance drug with mean terminal half-life between 7 to 11 hours.[8] Approximately two thirds metabolized via cytochrome P450 (CYP) enzymes (Cyp3A4 and CYP2J2) and CYP independent mechanisms, with one-third excreted as unchanged drug in urine.[8]

METHODS

A total of 60 patients who underwent elective primary total knee arthroplasty were included in this study. Inclusion and exclusion criteria are mentioned in table 1. All patients underwent primary total knee arthroplasty under regional anaesthesia with tourniquet application under strict aseptic precautions. No drains were used, compressive bandages were applied after wound closure before tourniquet release. All the operated cases were cemented with cruciate retaining prosthesis. The mean operative time was 120 minutes without any intra-op events. Oral Rivaroxaban 10 mg was given after 6 - 8 hours after wound closure.

All the patients were mobilized on post op day 1 (day of surgery being day 0). Oral rivaroxaban 10 mg, once daily dose was continued for 14 days All the patients were closely monitored for signs and symptoms of DVT, PE. Wells DVT criteria[9] was used to assess DVT in all the patients. Venous Doppler was done in suspected cases (well score > 2). Pulmonary embolism was assessed using Gurd and Wilson criteria[10] and CT Pulmonary angiogram was done in suspected cases. The primary efficacy outcome was the composite of any deep-vein thrombosis, non-fatal pulmonary embolism, or death from any cause Up to day 17 after surgery. The main secondary efficacy outcome was major venous thromboembolism (i.e., proximal deep-vein thrombosis, non-fatal pulmonary embolism, or death related to venous thromboembolism).[7]

Major bleeding was defined as clinically overt bleeding that was fatal, occurred in a critical organ necessitated operation, was outside of the surgical site and associated with a fall in haemoglobin of 2 g/dL or more (calculated from the postoperative haemoglobin baseline value before the event), or required an infusion of two or more units of blood. One of the secondary safety outcomes was clinically relevant non-major bleeding, defined as multiple-source bleeding, unexpected haematoma (>25 cm^2), excessive wound haematoma, nose bleeding (>5 min), gingival bleeding (>5 min), macroscopic haematuria, rectal bleeding, coughing or vomiting blood, vaginal bleeding, blood in semen, intra-articular bleeding with trauma, or surgical-site bleeding.[7] In patients with symptoms in both legs, the more symptomatic leg is used.

Inclusion Criteria	Exclusion Criteria
Patients aged > 18 yrs.	Patients with known coagulopathies
Unilateral or bilateral primary total knee arthroplasty patients	Severe renal impairment, liver disease
	Patients on anti-retro viral therapy
	History of thromboembolic disease

Table 1. Inclusion and Exclusion Criteria

Clinical Feature	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilisation of the lower extremities	1
Recently bedridden for more than 3 days or major surgery, within 4 weeks	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting oedema (greater in the symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely or greater than that of deep-vein thrombosis	-2

Table 2. Wells DVT Criteria- Clinical Model for Predicting Pre-Test Probability for Deep-Vein Thrombosis[9]

Statistical Analysis

Data was entered into Microsoft excel data sheet and was analysed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Continuous data was represented as mean and standard deviation.

RESULTS

In the study majority of subjects were in the age group <60 years (46.7%), 70% were females and 30% were males, 48.3% were overweight, 33.3% were obese grade I and 3.3% were obese grade II. 15% had DM, 51.7% had HTN, 33.3% had obesity, 6.7% had Asthma or COPD, 11.7% had IHD, 3.3% had PSOR. 78.3% had OA, 3.3% had PA and

18.3% had RA, 46.7% were left side and 53.3% were right side.

		Count	%
Age	<60 years	28	46.7%
	61 to 70 years	25	41.7%
	>70 years	7	11.7%
Sex	Female	42	70.0%
	Male	18	30.0%
BMI	Normal (18.5 to 24.9)	9	15.0%
	Overweight (25 to 29.9)	29	48.3%
	Obese I (30 to 34.9)	20	33.3%
	Obese II (35 to 39.9)	2	3.3%
DM	Present	9	15.0%
HTN	Present	31	51.7%
Obesity	Present	20	33.3%
Asthma or COPD	Present	4	6.7%
IHD	Present	7	11.7%
PSOR	Present	2	3.3%
Indications	OA	47	78.3%
	PA	2	3.3%
	RA	11	18.3%
Side	Left	28	46.7%
	Right	32	53.3%

Table 3. Profile of Subjects Undergoing Total Knee Replacement

A total of 60 patients were studied in the study period where all the 60 patients received Oral rivaroxaban 10 mg once daily dose. In the study majority of subjects were in the age group <60 years (46.7%), 70% were females and 30% were males, 48.3% were overweight, 33.3% were obese grade I and 3.3% were obese grade II. 15% had DM, 51.7% had HTN, 33.3% had obesity, 6.7% had Asthma or COPD, 11.7% had IHD, 3.3% had PSOR. 78.3% had OA, 3.3% had PA and 18.3% had RA, 46.7% were left side and 53.3% were right side.

None of the patients had a family history of coagulopathy. None of the patients had previous hospital admissions for stroke / IHD. Outcomes of the TKA were measured by Knee Society scoring system and Oxford knee score. All the patients were followed up for a period of 14 days in hospital and later regular follow up done at 4 weeks, 6 weeks and 12 weeks. In the study 1.6% had DVT, none of the subjects had Non-fatal pulmonary embolism, Major bleeding and Minor bleeding.

		Count	%
Venous Thromboembolism	DVT	1	1.6%
	No	59	98.4%
Non-fatal pulmonary embolism	No	60	100%
Major bleeding	No	60	100%
Minor bleeding	No	60	100%

Table 4. Complications among Subjects

Deep Vein Thrombosis

One patient among population of 60 patients developed left calf tenderness on post op day 7. Assessed according to wells score and later ultrasound venous Doppler was done which revealed non compressibility of superficial veins with thrombus not extending into inferior vena cava.

Bleeding Manifestations

All the patients were monitored for oral and gastric bleeding episodes and postoperative haemoglobin levels were assessed to know the reduction in value.

DISCUSSION

The use of thromboprophylaxis after major orthopaedic surgeries is a common practice ever since the latest NICE guidelines were published. In randomised, double blinded, phase III study involving 3148 patients undergoing knee arthroplasty in RECORD 4 trial. Oral, once daily rivaroxaban 10 mg was more efficacious and significantly superior to subcutaneous enoxaparin 30 mg for the prevention of venous thromboembolism after total knee arthroplasty. Without significant difference in the risk of major or clinically relevant bleeding.[7]

In our study we studied the efficacy of Oral rivaroxaban 10 mg once daily dose after elective total knee arthroplasty in 60 patients in the time period of August 2018- December 2019. The timing of the first dose of anticoagulant is still controversial. We followed early post-operative initiation of rivaroxaban according to RECORD 4 trial.[7] Our study highlights the potential benefits and risk associated with the use of rivaroxaban as the drug of choice for thromboprophylaxis. The ease of administration of oral agents like rivaroxaban compared to subcutaneously give agents like Enoxaparin will lead to better patient compliance and early discharge from hospital.

The importance of prevention of Deep vein thrombosis, pulmonary embolism after major orthopaedic surgeries should be balanced against the potential surgical complications like oozing, infection, haematoma, stiffness and return to theatre. Our study was an independent attempt to evaluate these parameters and has demonstrated both the advantages as well as disadvantages. Once daily oral rivaroxaban 10 mg for 14 days is an effective agent in reducing number of cases of deep venous thrombosis after total knee arthroplasty with good patient compliance.

CONCLUSIONS

Once daily oral dose of rivaroxaban 10 mg for 14 days is an effective modality in reducing the number of cases of VTE after Total Knee Arthroplasty. Our study highlights the potential benefits and risks associated with the use of rivaroxaban for thromboprophylaxis. The ease of administration of oral agents compared to subcutaneously given agents like Enoxaparin will lead to better patient compliance and early discharge from hospital.

Financial or Other Competing Interests: None.

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