|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
NLM (National Library of Medicine ID: 101738825)
Index Copernicus Value 2018: 75.71
Original Research Article
Volume 4, Issue 7; July: 2020; Page No. 82-85

RIVAROXABAN IN THE PROPHYLAXIS AGAINST VENOUS THROMBOEMBOLISM AFTER TOTAL KNEE ARTHROPLASTY- A PROSPECTIVE STUDY IN A TERTIARY CARE CENTRE

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Article Info: Received 18 June 2020; Accepted 11 July 2020
DOI: https://doi.org/10.32553/ijmbs.v4i7.1288
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Conflict of interest: No conflict of interest.

Abstract

Background: Venous thromboembolism (VTE) is a major healthcare problem that affects more than 1.6 million persons each year worldwide. Patients undergoing major orthopedic surgery, total knee arthroplasty (TKA), and total hip arthroplasty (THA) are at high risk for developing VTE, which can manifest as deep vein thrombosis (DVT) or pulmonary embolism (PE), and PE can be life-threatening. It is a preventable complication of in-hospital mortality.

The prophylaxis to prevent VTE varies from vitamin K antagonists like warfarin, low molecular weight heparin like enoxaparin, Fondaparinox sodium, direct factor Xa inhibitor like rivaroxaban and apixiban, mechanical thromboprophylaxis.

Materials and Methods: Presented is a prospective study to see the efficacy of Oral rivaroxaban 10mg once daily dose for 14 days in the prevention of VTE in 60 elective cases total knee arthroplasty. The study was done from June 2017- October 2018 in the department of orthopaedics, Prathima institute of medical sciences, Nagunur, Karimnagar. All the operated cases were cemented with cruciate retaining prosthesis. Oral Rivaroxaban 10mg 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 evaluated with modified Gurd and Wilson criteria and subsequent CT pulmonary angiogram.

Results: In study involving 60 primary total knee replacement cases, only one patient developed deep venous thromboembolism (1.6%) with oral Rivaroxaban. No cases of bleeding manifestations or pulmonary embolism were reported.

Conclusion: once daily oral dose of rivaroxaban 10mg for 14 days is an effective modality in preventing the number of cases of VTE after Total knee arthroplasty. 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.

Key words: Venous thromboembolism, Total knee arthroplasty, Rivaroxaban, Deep vein thrombosis, Pulmonary embolism

Introduction

Venous thromboembolism is not uncommon and is a potential complication after major orthopaedic surgeries like Total knee Arthroplasty, 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, Fondaparinox sodium, direct factor Xa inhibitor like rivaroxaban and apixiban, 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[(8)]. Orally 10mg tablet once daily for 14 days is used in preventing VTE after Total knee arthroplasty. [(7)]

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)]

Materials and methods

The study was done from June 2017- October 2018. A total of 60 patients who underwent elective primary total knee

arthroplasty in department of orthopaedics, Prathima institute of medical sciences, Nagunur, Karimnagar, Telangana India, were included in this study. Inclusion and exclusion criteria are mentioned in table 1

Table 1:

Inclusion criteria	Exclusion criteria
Pateints aged > 18yrs	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

All Patients underwent primary total knee arthroplasty under regional anaesthesia with tourniquet application under strict aseptic precautions. Drains were not 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 10mg was given after 6-8 hours after wound closure. All the patients were mobilized on post operative day 1. Oral rivaroxaban 10mg, 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]

Table 2: wells DVT criteria-clinical model for predicting pretest probability for deep-vein thrombosis

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

In patients with symptoms in both legs, the more symptomatic leg is used.

1. Statistical analysis:

Data was entered into Microsoft excel data sheet and was analyzed 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.

Table 3: Profile of subjects undergoing Total Knee Replacement

		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%

Results

A total of 60 patients were studied in the study period where all the 60 patients received Oral rivaroxaban 10mg 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.

Table 4: Complications among subjects

		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%

In the study 1.6% had DVT; none of the subjects had Non-fatal pulmonary embolism, Major bleeding and Minor bleeding.

Deep Vein Thrombosis

One patient among population of 60 patients developed left calf tenderness on 7th post op day . Assessed according to wells score and later ultrasound venous Doppler was done which revealed non compressibility of superficial veins with thrombus which was 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. Rivaroxaban has predictable pharmacokinetics, a rapid onset of action and high oral bioavailability.

In randomised, double blinded, phase III study involving 3148 patients undergoing knee arthroplasty in RECORD 4 trial. Oral, once daily rivaroxaban 10mg 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 10mg 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] Chen et al believed that rivaroxaban has the major advantages of no required laboratory monitoring and once-daily oral dosing, giving it the opportunity to replace current antithrombotics on the market today[11] For VTE prophylaxis in patients undergoing total knee replacement in Canada, rivaroxaban is a cost-effective alternative to enoxaparin, providing more quality-of-life benefit at a lower cost[12]. Ryttberg et al presented an economic model showing that rivaroxaban is a cost-effective alternative to 14 days of LMWH for VTE prophylaxis over a 5-year period in Sweden[13]. Turpie et al[33] found that rivaroxaban reduces all-cause mortality and symptomatic VTE compared with enoxaparin regimens after elective TKA[14].

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.

Conclusion:

Once daily oral rivaroxaban 10mg for 14 days is an effective agent in reducing number of cases of deep venous thrombosis after total knee arthroplasty with good patient compliance.

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