Original Article

Efficacy and Safety of Rivaroxaban as Thromboprophylaxis after Arthroplasty of the Hip or Knee

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ABSTRACT

Objective: to investigate efficacy and safety of rivaroxiban as thromboprophylaxis in major orthopedic surgeries.
Study Design: Non randomized experimental trial study
Place and Duration of Study: This study was conducted at the department of orthopedic surgery, Bahawalpur Victoria Hospital, Bahawalpur, from April 2017 to April 2018.
Materials and Methods: Adult patients of age limit from 20 to 45 years who were selected for hip and knee arthroplasty and who were given Rivaroxiban 10 mg were included in the study. Three main outcome variables were investigated: VTE confirmed through imaging, major bleed and death. SPSS version was used to analyze data. P value ≤ 0.05 was considered as significant.
Results: A total number of 32 patients included in this study. Our results show that no patient was died during rivaroxiban treatment in our study duration but VTE was observed in 6% of cases and major bleed was observed in 15% of cases. Except these major variables mean age, hemoglobin, platelets, PT, APTT, urea, creatinine and bilirubin of the patients was 45.50±0.71 years, 103.51±2.12 g/l, 227.0±0.21×10^9/l, 13.50±2. 14s,23.50± 4.51s,4.50±1.78mmol/l, 68.0±2.83 µmol/l and 11.50±2.57 µmol/l respectively
Conclusion: Results of our study revealed that rivaroxiban is a safe drug as mortality is zero during its treatment and its is also effective as it's reduce the incidence of VTE and major bleeding when used as thromboprophylaxis during surgery of hip arthroplasty and knee arthroplasty.
Key Words: Rivaroxaban, Thromboprophylaxis, Arthroplasty, Efficacy, Safety.

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INTRODUCTION

Deep venous thrombosis DVT is a serious complication after orthopedic surgeries like hip and knee replacement[1,2]. It may lead to pulmonary embolism which is a more sever condition. After proper thrombophylaxis with thrombolytic agents like low molecular weight heparin and inhibition with factor Xa and IIa it was reported in previous Meta analysis that 0.5% of cases can be go on after hip arthroplasty and 0.1% after knee arthoplasty[3,4]. These portions were found before hospital discharge of patients. Among inhibitors of factor Xa, Rivaroxiban is general agent used for prevention of DVT after major orthopedic surgeries[5]. This agent was introduced by national Institute for health and care excellence in year of 2009. Rivaroxiban can be given orally for 35 days after hip replacement surgery and for 14 days after knee replacement surgery[6]. Use of Rivaroxiban was recommended after four clinical trials in which it was compared with enoxaparin and all these four studies were multicenter[7]. Results revealed that DVT and PE was occurd in 1.1% and 3.7% after hip arthoplasty and 9.6% and 18.9% after knee arthoplasty. In all these trials Rivaroxiban found to be superior as compared to enoxaparin[8]. Dose wise comparison of both drugs also find out that Rivaroxiban OD dose is superior to BD dose of enoxaparin[9]. Results of these four trials were sufficient for recommendation of Rivaroxiban as thromboprophylaxis when major orthopedic surgeries were performed[10]. Studies conducted on this topic before were having their own limitations. Aim of our study is to investigate the safety and efficacy of Rivaroxiban as athromboprophylaxis after hip and knee arthoplasty. Our study is single centered.

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MATERIALS AND METHODS

This cross sectional study was conducted in the department of orthopedic surgery, Bahawalpur Victoria

Hospital, Bahawalpur, from April 2017 to April 2019. Study was started after informed consent from patients and approval from hospital ethical committee. A total number of 32 patients included in this study. Sample size was calculated from WHO calculator for sample size calculations and non probability consecutive sampling technique was used. Adult patients of age limit from 20 to 45 years who were selected for arthoplasty and who were given Rivaroxiban 10 mg were included in the study.

Three primary outcomes were assessed in these patients, VTE confirmed through imaging, no bleeding, major bleeding episodes and death. Major bleeding was defined as fall in hemoglobin less than or equal 20 g/l or 2 pints blood transfusion. This criteria was recommended by control of anticoagulation subcommittee of international society on thrombosis and hemostasis. Return of patients to the theater for reopen and surgical site bleed also labeled under major bleeding. Any other type of bleeding labeled as non major or minor bleeding. Follow up started from the day of discharge from hospital and outcome measured with the end of DVT till last follow up.

Data was analyzed by using SPSS version 24, mean and SD was calculated for numerical variables like age, urea creatinine, bilirubin, PT, APTT and frequency and percentages were calculated for categorical data like gender, VTE, major bleeding, death. Student that test was applied for association of numerical variable and Chi square test used for categorical variables association. P value less than or equal to 0.5 was considered to be significant.

RESULTS

A total number of n=32 patients were included in this study, both gender. Gender distribution revealed as (34.4%) n=11 males and (65.6%) n=21 females. The mean age, hemoglobin, platelets, PT, APTT, urea, creatinine and bilirubin of the patients was 45.75±1.04 years, 105.1±2.10 g/l, 232.25±3.49×10^9/l, 10.22± 1.79s,24.53±2.14s,4.84±1.71mmol/l, and 68.89± 4.35 µmol/l and11.22±1.18 µmol/l respectively. Hip arthroplasty and knee arthroplasty was observed as (37.5%) n=12 and (40.6%) n=13 respectively. Hypertension, diabetes mellitus, ischemic heart disease, chronic kidney disease, ACEI/ARB, gastric protection, aspirin and anticoagulation was noted as (68.8%) n=22, (12.5%) n=4, (12.5%) n=4, (9.4%) n=3, (18.8%) n=6, (25%) n=8, (15.6%) n=5, (3.1%) n=1 respectively. (Table I).

There were (60%) n=3 male and (40%) n=2 female. The mean age, hemoglobin, platelets, PT, APTT, urea, creatinine and bilirubin of the patients was 46.0±1.24 years, 104.80±2.18 g/l, 229.80±3.89×10^9/l, 11.60±1.94 s, 23.80±2.19s, 4.60±0.89mmol/l, 66.20±3.03 µmol/l and 11.80±0.85 µmol/l respectively. Hip arthroplasty was observed as (40%) n=2. Hypertension, diabetes mellitus, aspirin and anticoagulation was noted as (40%) n=2, (40%) n=2, (20%) n=1, and (20%) n=1 respectively.

There were (29.6%) n=8 male and (70.4%) n=19 female. The mean age, hemoglobin, platelets, PT, APTT, urea, creatinine and bilirubin of the patients was 45.70±1.12 years, 105.15±2.12 g/l, 232.72±3.29×10^9/l, 9.96±1.67 s, 24.66±2.19 s, 4.88±1.82 mmol/l, 66.33±3.03 µmol/l and 11.11±1.22 µmol/l respectively. Hip arthroplasty was observed as (40.7%) n=11. Hypertension, diabetes mellitus, aspirin and anticoagulation was noted as (74.1%) n=20, (11.1%) n=3, (14.8%) n=4, and (0%) n=0 respectively.

No death was recorded for bleed and not bleeds respectively. The differences were statistically insignificant except anticoagulation (p=0.018). (Table 2).

There were (50%) n=1 male and (50%) n=1 female. The mean age, hemoglobin, platelets, PT, APTT, urea, creatinine and bilirubin of the patients was 45.50±0.71 years, 103.51±2.12 g/l, 227.0±0.21×10^9/l, 13.50± 2.14s,23.50±4.51s,4.50±1.78mmol/l, 68.0±2.83 µmol/l and 11.50±2.57 µmol/l respectively. Hip arthroplasty was observed as (50%) n=1. Hypertension, diabetes mellitus, aspirin and anticoagulation was noted as (50%) n=1, (50%) n=1, (50%) n=1, and (0%) n=0 respectively.

Table No.1: Patient characteristics, procedural information and Blood results in the inpatient setting

Variable	Presence
Age (years)	45.75±1.04
Gender	
Male	(34.4%) n=11
Female	(65.6%) n=21
Procedure	
Hip arthroplasty	(37.5%) n=12
Knee arthroplasty	(40.6%) n=13
Medical History	
Hypertension	(68.8%) n=22
Diabetes mellitus	(12.5%) n=4
Ischemic heart disease	(12.5%) n=4
Chronic kidney disease	(9.4%) n=3
Medication History	
ACEI/ARB	(18.8%) n=6
Gastric protection	(25%) n=8
Aspirin	(15.6%) n=5
Anticoagulation	(3.1%) n=1
Blood results upon hospital discharge	
Hemoglobin (g/l)	105.1±2.10
Platelets (×10^9/l)	232.25±3.49
PT (s)	10.22±1.79
APTT (s)	24.53±2.14
Urea (mmol/l)	4.84±1.71
Creatinine(µmol/l)	68.89±4.35
Bilirubin(µmol/l)	11.22±1.18

There were (33.3%) n=10 male and (66.7%) n=20 female. The mean age, hemoglobin, platelets, PT, APTT, urea, creatinine and bilirubin of the patients was 45.76±1.08 years, 105.20±2.09 g/l, 232.60±3.31×10^9/l, 10.12±1.62 s, 24.60±2.19 s, 4.86±1.75 mmol/l, 66.20±3.01 µmol/l and 11.20±1.21 µmol/l respectively. Hip arthroplasty was observed as (40%) n=12. Hypertension, diabetes mellitus, aspirin and anticoagulation was noted as (70%) n=21, (13.3%) n=4, (13.3%) n=4, and (3.3%) n=1 respectively.

No death was recorded for ATE and no ATE respectively. The differences were statistically insignificant except PT (p=0.005). (Table 3).

Table No.2: Factors associated with bleeding events on treatment or within 48 hours of stopping Rivaroxaban

Variables	Bleed (15%) n=5	No Bleed (85%) n=27	P Value
Gender			
Male	(60%) n=3	(29.6%) n=8	0.189
Female	(40%) n=2	(70.4%) n=19	
Age (years)	46.0±1.24	45.70±1.12	0.570
Elective			
Hip arthroplasty	(40%) n=2	(40.7%) n=11	0.975
Medical History			
Hypertension	(40%) n=2	(74.1%) n=20	0.131
Diabetes mellitus	(40%) n=2	(11.1%) n=3	0.102
Medication History			
Aspirin	(20%) n=1	(14.8%) n=4	0.769
Anticoagulation	(20%) n=1	(0%) n=0	0.018
Blood results upon hospital discharge			
Hemoglobin (g/l)	104.80± 2.18	105.15±2.12	0.740
Platelets (×10^9/l)	229.80± 3.89	232.72± 3.29	0.088
PT (s)	11.60±1.94	9.96±1.67	0.056
APTT (s)	23.80±2.19	24.66±2.19	0.414
Urea (mmol/l)	4.60±0.89	4.88±1.82	0.734
Creatinine (µmol/l)	66.20±3.03	66.33±3.03	0.238
Bilirubin (µmol/l)	11.80±0.85	11.11±1.22	0.238
Death	(0%)n=0	(0%)n=0	1.0

Table No.3: Factors associated with off-treatment VTE events after completion of a course of Rivaroxaban

Variables	VTE (6%) n=2	No VTE (94%) n=30	P Value
Gender			
Male	(50%) n=1	(33.3%) n=10	0.631
Female	(50%) n=1	(66.7%) n=20	
Age (years)	45.50±0.71	45.76±1.08	0.275
Elective			
Hip arthroplasty	(50%) n=1	(40%) n=12	0.780
Medical History			
Hypertension	(50%) n=1	(70%) n=21	0.555
Diabetes mellitus	(50%) n=1	(13.3%) n=4	0.167
Medication History			
Aspirin	(50%) n=1	(13.3%) n=4	0.167
Anticoagulation	(0%) n=0	(3.3%) n=1	0.793
Blood results upon hospital discharge			
Hemoglobin (g/l)	103.51±2.12	105.20±2.09	0.275
Platelets (×10^9/l)	227.0±0.21	232.60±3.31	0.025
PT (s)	13.50±2.14	10.12±1.62	0.005
APTT (s)	23.50±4.51	24.60±2.19	0.491
Urea (mmol/l)	4.50±1.78	4.86±1.75	0.774
Creatinine(µmol/l)	68.0±2.83	66.20±3.01	0.481
Bilirubin(µmol/l)	11.50±2.57	11.20±1.21	0.735
Death	(0%)n=0	(0%)n=0	1.0

DISCUSSION

In Pakistan our study is first one to plan and investigate the efficacy and safety of rivaroxiban as thromboprophylactic agent in major orthopedic surgeries like hip and knee arthroplasty. No patient was died during Rivaroxibn treatment in our study duration but VTE was observed in 6% of cases and bleed was observed in 15% of cases.

In a study conducted by Eriksson BI et al[11] death was reported in 0.3% VTE in 0.2% of patients and major bleeding was occurred in 0.3% of cases, results of this study almost identical to our study. In this study rivaroxiban was compared with enoxaparin and rivaroxiban labeled as more safe and efficacious drug to prevent VTE events after major orthopedic surgeries. This study can be compared with our study.

Another study was conducted on this topic in year 2008 by Kakkar AK et al[12] and reported 2% death cases and 6.6 % of major bleeding events with p=0.0001% and confidence interval 95%. In this study death events are much higher and bleeding events are almost same as our study. This trial was conducted on 864 patients who

were given rivaroxiban and in other group 869 patients were given enoxaparin. Safety and efficacy of rivaroxiban was accepted. This study can also be compared with our study.

In another conducted by Michael R et al[13] death was not reported in any patient and VTE was observed in 1.0% of patients with P=0.01 and absolute risk reduction, 1.6%; 95% CI, 0.4 to 2.8, major bleeding events were observed 0.6%. Results of this trial were also similar to our study, so this study is also comparable with our study.

Turpie AG et al[14] conducted a study in 2009 and concluded that rivaroxiban is better than enoxaparin in aspects of mortality, VTE and major bleeding. According to his results primary outcome (deep vein thrombosis) was 6.9% which almost equal to our results, secondly major bleeding was reported 0.7%, in another similar study Sindali K et al[15] also reported that rivaroxiban is effective and safe to reduce VTE and mortality rate after hip replacement and knee replacement surgeries. These two studies also go into the favor of our study.

In a study conducted by Jameson SS et al[16] reported 0.72 % VTE within 90 days of rivaroxiban treatment, he compared rivaroxiban with low molecular weight heparin. Rivaroxiban have 0.36% pulmonary embolism and heparin have 0.55% PEs with 95% CI and odds ratio 1.52. In another study Patel MR et al[17] also reported similar findings as VTE occurred in 14.9% of patients and major bleeding occurred in 0.2% of patients.

Furthermore Samama CM et al[18] and Chandrasekaran S et al[19] also conducted studies on this topic for evaluation of efficacy and safety of rivaroxiban and reported that rivaroxiban is a better drug for thromboprophylaxis in major orthopedic surgeries like hip and knee replacement as compare to any drug used for this purpose. Conclusion of his observation is also similar as our study.Lassen MR et al[20] also use rivaroxiban for this purpose but he compare its role between the groups (knee replacement and hip replacement) his observation revealed that there was not a significant difference among the groups about surgical events and VTE and PEs when rivaroxiban is used.

CONCLUSION

Results of our study revealed that rivaroxiban is a safe drug as mortality is zero during its treatment and it is also effective as it's reduce the incidence of VTE and major bleeding when used as thromboprophylaxis during surgery of hip arthroplasty and knee arthroplasty.

Author's Contribution:

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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