

Comparative study between Aspirin and Oral anticoagulant for VTE Prophylaxis after Knee Arthroplasty

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ABSTRACT

Background:

Osteoarthritis is one of the most common diseases that affect the geriatric population. Most patients suffering from severe osteoarthritis undergo knee arthroplasty.

Objective:

This study aims to assess the effectiveness and safety of Aspirin as a prophylaxis of venous thromboembolism compared with the direct oral anticoagulant after total knee arthroplasty.

Patients and Methods:

This is a prospective study that targets a convenient sample that included 40 patients. The study included all patients admitted to Menoufia University Hospital and Om Elmasrien hospital to have primary total knee arthroplasty from April 2019 to December 2019. Patients were alternatively and randomly divided into two groups:

Group (1) received Rivaroxaban 10 mg oral per day for 14 days starting from postoperative day 1.

Group (2) received Aspirin 81 mg oral per day for 14 days starting from postoperative day 1.

All patients were assessed pre and postoperative for clinical and radiological manifestations of DVT.

Results:

The present study revealed that the mean age of the patients in the rivaroxaban group was 60.30 ± 5.85 years whereas, in the aspirin group, it was 63.20 ± 4.61 years. Females represented 90% of the patients in both groups and 100% of the patients in both groups were non-smokers. The affected side was the left side in 80% of the patients in the rivaroxaban group; meanwhile, it was the right side in 60% of the patients in the aspirin group. The incidence of DVT was found only 5% in the rivaroxaban group and 0% in the aspirin group.

Conclusion:

Aspirin can be considered a safe and effective agent in the prevention of VTE, and aspirin was not significantly different from the oral anticoagulant rivaroxaban for the prevention of DVT or pulmonary embolism after total knee arthroplasty.

Keywords:

Aspirin - Oral Anticoagulant - Knee Arthroplasty.

INTRODUCTION

Osteoarthritis is one of the most common diseases that affect the geriatric population. Most patients suffering from osteoarthritis undergo non-operative treatment at first. Severe cases of knee osteoarthritis eventually need to have Total Knee Arthroplasty (TKA), after conservative treatment has failed. TKA was found to provide pain improvement, better mobilization, and quality of life. During the last few decades, the number of arthroplasties increases each year.⁽¹⁾

On the other hand, Patients undergoing an arthroplasty are at risk of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE). In the absence of prophylaxis, VTE may occur in more than 35% of patients undergoing arthroplasty. However, most are asymptomatic.

Because of the relatively high incidence of VTE, prophylaxis has been recommended after arthroplasty.^(2,3)

The best agents and optimum protocols to minimize VTE under these circumstances are not known. The most recent American Academy of Orthopedic Surgeons and American College of Chest Physicians guidelines outline prophylaxis options including aspirin (ASA), warfarin, heparin-based drugs, and other direct oral anticoagulants (DOAC) but do not guide how to individualize VTE prophylaxis.^(2,4) Although there are many chemical agents for VTE prophylaxis, there is a difference in their efficacy and the risk of bleeding. The choice of the agent therefore relies on a balance between the desire to minimize VTE and the attempt to reduce the risk

of bleeding, with its undesirable and occasionally fatal consequences.⁽⁵⁾

The direct oral anticoagulants are commonly prescribed for extended prophylaxis because of their effectiveness, safety, and convenience of use.^(6,7)

Acetylsalicylic acid, which is generally known as aspirin, is an agent for the prevention of VTE following arthroplasty. Many studies have reported its efficacy in minimizing VTE following arthroplasty.^(8,9) In recent years, there has been a dramatic shift, at least in North America, towards the use of aspirin as the main modality for VTE prophylaxis following arthroplasty. A recent poll of > 1200 attendees of the annual meeting of the American Association of Hip and Knee Surgeons, in 2016, revealed that > 80% use aspirin as the main prophylaxis in their patients undergoing arthroplasty of the hip or knee.^(10,11)

There are various reasons for the popularity of aspirin as a prophylactic agent. Besides the proven efficacy, it is inexpensive and well-tolerated, and its use does not require routine blood monitoring.^(12,13) It is also a 'milder' agent that is unlikely to result in hematoma formation, which may require further surgery, and which increases the risk of infection.⁽¹⁴⁾ Aspirin is also less likely to be associated with persistent wound drainage, with all its undesirable consequences, than agents such as low-molecular-weight heparin (LMWH) or other more aggressive agents.^(15,16)

We studied the effectiveness and safety of extended prophylaxis with aspirin as compared with the direct oral anticoagulant for the prevention of venous thromboembolism after total knee arthroplasty.

PATIENTS AND METHODS

Study design

This is a prospective study that targets a convenient sample which included (40) patients. The study included all patients admitted to Menoufia University Hospital and Om Elmasrien hospital to have primary total knee arthroplasty from April 2019 to December 2019. Patients were alternatively and randomly divided into two groups:

Group (1) received Rivaroxaban 10 mg oral per day for 14 days starting from postoperative day 1.

Group (2) received Aspirin 81 mg oral per day for 14 days starting from postoperative day 1.

Inclusion criteria:

All Patients who were admitted to the hospital to have primary total knee arthroplasty.

Exclusion criteria:

1. History of previous VTE.
2. Prominent varicose vein.
3. Cardiac patient on a pre-operative regimen of anticoagulant e.g. warfarin.
4. Revision knee arthroplasty.
5. Restricted weight bearing after TKA.

Methods

All patients included in this study had preoperative, operative, and postoperative data collection.

A) Preoperative data: include

- 1) **History taking** included the history of medical disease, drug intake, venous thromboembolism, and previous orthopedic operation.
- 2) **The general assessment** included height, body weight, body mass index, presence of lower limb varicose vein, and vascular insufficiency symptoms.
- 3) **Laboratory assessment:** complete blood count, liver function test, serum creatinine, and international normalizing ratio (INR).
- 4) Explanation of details of the study and informed consent.

B) Operative data:

All operative details were recorded including the type of anesthesia (spinal), and the surgical approach is medial Para patellar approach, type of total knee prosthesis, the volume of blood loss, and antibiotics started one hour preoperative and postoperative for 5 days.

C) Post-operative data:

Day (1-14) post-operative:

The Rivaroxaban group received 10 mg rivaroxaban 12 hours after surgery and then once daily for 14 days.

The Aspirin group received 81mg aspirin in the evening or the next day after surgery and then once daily for 14 days.

Also, observation of the patient general condition, amount of blood loss in the drain, and result of the post-operative CBC, according which we could determine their needs for blood transfusion, the volume of blood transfusion, wound condition, tenderness, swelling or pitting edema of the lower limb, ischemic stroke, non-fatal pulmonary embolism, and unexplained death. Any side effect of the drug during the course therapy was recorded (major bleeding, minor bleeding, vomiting or allergy). The drain was evacuated every 24 hours and removed after 48 hours.

Patients were followed up for at least 3 days postoperative in the hospital for bleeding and calf pain or swelling and bilateral lower limb venous

duplex if there is any clinical suspicion of deep venous thrombosis at any time.

Day (15):

The patients were clinically reassessed on the 15th day post-operative before having duplex US. The assessment was carried to assess the wound condition, tenderness, swelling or pitting edema of the lower limb, major bleeding, minor bleeding, ischemic stroke, non-fatal pulmonary embolism.

Duplex US was done on the 15th day post-operative for all patients.

Duplex ultrasonography is a simplified technique used for quick deep vein thrombosis diagnosis; it has both high sensitivity and specificity for detecting deep vein thrombosis.

One month postoperative:

Clinical reassessment for detection of early postoperative complications.

Three months postoperative:

Reassessment of the patients again three months after surgery for tenderness, swelling, or pitting edema of the lower limb, major bleeding, minor bleeding, ischemic stroke, non-fatal pulmonary embolism, and unexplained death.

Ethical consideration:

1. Any unexpected risks that appeared during the research were cleared to participants and the ethical committee on time.
2. Informed consent was obtained from all participants in this research.
3. Privacy of participants and confidentiality of the data was maintained.
4. No photos were taken of the participant.
5. There are no hazards of this research on the environment or the participants.

RESULTS

Demographic data of rivaroxaban and aspirin groups (Table 1):

For the rivaroxaban group; the age of the patients was 60.30 ± 5.85 , 18 (90 %) females and 2 (10 %) males, all were non-smokers, and 16 (80 %) patients with the left side and 4 (20 %) patients with the right side.

For the aspirin group; the age of the patients was 63.20 ± 4.61 , 18 (90 %) females and 2 (10 %) males, all were non-smokers, and 8 (40 %) patients with the left side and 12 (60 %) patients with the right side. There was a non-significant difference in the age between both groups.

Table (1): Demographic data of rivaroxaban and aspirin groups

Variables	Rivaroxaban group	Aspirin group
Individuals, n	20 (100 %)	20 (100 %)
Age (yr)		
54 – 63	16 (80 %)	12 (60 %)
≥ 63 – 72	4 (20 %)	8 (40 %)
Mean ± SD	60.30 ± 5.85	63.20 ± 4.61
Gender		
Females	18 (90 %)	18 (90 %)
Males	2 (10 %)	2 (10 %)
BMI		
	30.59 ± 4.35	27.80 ± 4.12
Smoking habit		
Non-Smokers	20 (100 %)	20 (100 %)
Smokers	0 (0 %)	0 (0 %)
Side		
Left	16 (80 %)	8 (40 %)
Right	4 (20 %)	12 (60 %)

Comorbidities (Table 2)

In the rivaroxaban group, bronchial asthma was recorded in 2 patients (10 %) and hypertension was recorded in 2 patients (10 %). However, in the Aspirin group, hypertension was recorded in 6 patients (30 %), hypothyroidism was recorded in 2 patients (10 %), and ischemic heart disease was recorded in 2 patients (10 %).

Table (2): Comorbidities

Variables	Rivaroxaban group (n = 20)	Aspirin group (n = 20)	Chi-square value	P-value
Bronchial asthma			-	-
Yes	2 (10 %)	0 (0 %)		
No	18 (90 %)	20 (100 %)		
Hypertension			0.234	0.629
Yes	2 (10 %)	6 (30 %)		
No	18 (90 %)	14 (70 %)		
Hypothyroidism			-	-
Yes	0 (0 %)	2 (10 %)		
No	20 (100 %)	18 (90 %)		
Ischemic heart disease			-	-
Yes	0 (0 %)	2 (10 %)		
No	20 (100 %)	18 (90 %)		

Pre-operative laboratory investigations (Table 3):

The table showed hemoglobin concentration, platelets count, and INR in both the Rivaroxaban group and the Aspirin group. There were non-significant differences in hemoglobin concentration, platelet count, and INR between both the Rivaroxaban group and the Aspirin group.

Table (3): Pre-operative laboratory investigations

Variables	Rivaroxaban group (n = 20)	Aspirin group (n = 20)	t-value	P-value
Hemoglobin (gm/dl)	12.27 ± 0.87	12.63 ± 1.24	- 1.067	0.293
Platelets (count X 10³/microliter)	210.40 ± 45.97	231.50 ± 48.38	- 1.414	0.166
INR	1.05 ± 0.05	1.03 ± 0.03	- 1.047	0.302

Post-operative clinical data (Table 4):

There were non-significant differences in edema of the lower limb, major bleeding, wound, and GIT bleeding between both the Rivaroxaban group and Aspirin group. However, there was a significant ($P < 0.05$) difference in minor bleeding between the Rivaroxaban group and Aspirin group, where 5 patients in the Rivaroxaban group had ecchymosis.

Table (4) Post-operative clinical assessment in both Rivaroxaban group and Aspirin group

	Rivaroxaban group (n = 20)	Aspirin group (n = 20)	Mann-Whitney	Z-value	P-value
Edema of lower limb			180.00	-0.874	0.382
Minimal	2 (10 %)	4 (20 %)			
Negative	18 (90 %)	16 (80 %)			
Minor bleeding			150.00	-2.360	0.018
Ecchymosis	5 (25 %)	0 (0 %)			
Negative	15 (75 %)	20 (100 %)			
Major bleeding			200.00	0.001	1.000
Positive	0 (0 %)	0 (0 %)			
Negative	20 (100 %)	20 (100 %)			
Wound			200.00	0.001	1.000
Infected	0 (0 %)	0 (0 %)			
Clean	20 (100 %)	20 (100 %)			
GIT bleeding			200.00	0.001	1.000
Positive	0 (0 %)	0 (0 %)			
Negative	20 (100 %)	20 (100 %)			

Post-operative thromboembolism (Table 5):

The table showed that pulmonary embolism did not occur in any of the included patients and that DVT occurred in only 5% of patients in the rivaroxaban group. However, no statistically significant differences were found between both groups as regards the postoperative incidence of DVT or pulmonary embolism

Table (5): Post-operative thromboembolism

	Rivaroxaban group (n = 20)	Aspirin group (n = 20)	Mann-Whitney	Z-value	P-value
Deep vein thrombosis (DVT)			180.00	-1.433	0.152
Positive	1 (5 %)	0 (0 %)			
Negative	19 (95 %)	20 (100 %)			
Pulmonary embolism			200.00	0.001	1.000
Positive	0 (0 %)	0 (0 %)			
Negative	20 (100 %)	20 (100 %)			

Table (5) showed a post-operative assessment in both the Rivaroxaban group and the Aspirin group. There were non-significant differences in Deep vein thrombosis (DVT), and pulmonary embolism between both the Rivaroxaban group and Aspirin group.

Three months of Post-operative (Table 6):

There were non-significant differences between both groups as regards the postoperative clinical data, the incidence of DVT, and pulmonary embolism.

Table (6): 3 months post-operative

	Rivaroxaban group (n = 20)	Aspirin group (n = 20)	Mann-Whitney	Z-value	P-value
Edema of lower limb			180.00	-1.433	0.152
Minimal	1 (5 %)	0 (0 %)			
Negative	19 (95 %)	20 (100 %)			
Minor bleeding			200.00	0.001	1.000
Ecchymosis	0 (0 %)	0 (0 %)			
Negative	20 (100 %)	20 (100 %)			
Major bleeding			200.00	0.001	1.000
Positive	0 (0 %)	0 (0 %)			
Negative	20 (100 %)	20 (100 %)			
Wound			200.00	0.001	1.000
Infected	0 (0 %)	0 (0 %)			
Clean	20 (100 %)	20 (100 %)			
GIT bleeding			200.00	0.001	1.000
Positive	0 (0 %)	0 (0 %)			
Negative	20 (100 %)	20 (100 %)			
Deep vein thrombosis (DVT)			180.00	-1.433	0.152
Positive	1 (5 %)	0 (0 %)			
Negative	19 (95 %)	20 (100 %)			
Pulmonary embolism			200.00	0.001	1.000
Positive	0 (0 %)	0 (0 %)			
Negative	20 (100 %)	20 (100 %)			

DISCUSSION

Major orthopedic surgery, mainly entailing hip fracture surgery, hip and knee arthroplasty, is associated with significant morbidity and mortality, which are especially attributable to the high risk of postoperative venous thromboembolism "VTE" (106) and VTE, including deep vein thrombosis "DVT" and pulmonary embolism, are major complications following total knee arthroplasty "TKA" and total hip arthroplasty "THA" (17). In the absence of thromboprophylaxis use, the incidence of DVT following a major orthopedic surgery has been noted to be as high as 40-60% after THA and 40-85% after TKA. These rates could be reduced to 1-10% with routine use of pharmacological thromboprophylaxis (18). Additionally, the incidence of pulmonary embolism without prophylaxis varies from 0.9-28% after THA and from 1.5-28% after TKA with a mortality rate of approximately 15% (19) and the risk persists for 3 to 6 months after surgery (20). Moreover, in a comparison cohort, THA was associated with an increased risk of VTE up to one year after surgery compared with the risks of the general population (21). Furthermore, VTE was found to be the most common cause of emergency readmission following lower limb arthroplasty (22). The hypercoagulable state usually starts on the operating table and persists for up to 12 weeks

after surgery⁽²³⁾. Reducing the rate of VTE via the use of mechanical and pharmacological prophylaxis will certainly reduce the overall mortality rate from fatal PE⁽²⁴⁾. The use of pharmacological thromboprophylaxis up to 35 days after THA and for at least 10 days after TKA is recommended by the American College of Chest Physicians guidelines⁽¹⁷⁾. A meta-analysis of data from randomized trials found that extended-duration prophylaxis after THA or TKA significantly reduced the frequency of post-discharge symptomatic VTE compared with placebo or untreated controls⁽²⁵⁾. The perioperative administration of anticoagulant prophylaxis has proved to reduce the rates of death and complications associated with venous thromboembolism after these procedures. Moreover, an additional benefit was observed by extending prophylaxis beyond hospital discharge, particularly after THA⁽²⁶⁾.

Direct oral anticoagulants are commonly prescribed for extended prophylaxis because of their effectiveness, safety, and convenience of use⁽²⁷⁾. Meanwhile, aspirin is an inexpensive, generic, and widely available antiplatelet drug. And 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⁽²⁸⁾.

This study was conducted aiming to assess the effectiveness and safety of aspirin as prophylaxis of venous thromboembolism compared with the direct oral anticoagulant after total knee arthroplasty.

The present study revealed that the mean age of the patients in the rivaroxaban group was 60.30 ± 5.85 years whereas in the aspirin group, it was 63.20 ± 4.61 years. Females represented 90% of the patients in both groups and 100% of the patients in both groups were non-smokers. The affected side was the left side in 80% of the patients in the rivaroxaban group; meanwhile, it was the right side in 60% of the patients in the aspirin group. The age range of patients included in this study comes in line with what was published by *Kuperman et al.*⁽²⁹⁾ in 2016 as they mentioned that TKA is a common and effective procedure for the treatment of end-stage osteoarthritis of the knee and that patients undergoing TKA are primarily geriatric. And as regards the higher percentage of females, this finding comes in line with what was published by *Lavernia*⁽³⁰⁾ as he mentioned that the percentage of patients undergoing TKA is biased more toward women than men and that in most areas

the percentage of female patients undergoing TKA is higher.

The present study revealed that both groups were comparable as regards the studied co-morbidities with no statistically significant differences between both groups as regards the prevalence of bronchial asthma, hypertension, hypothyroidism, or ischemic heart disease (**Table 2**). This balance in the baseline characteristics provides the basis for comparison between the study groups as it helps to minimize bias⁽³¹⁾.

The present study revealed that both groups were comparable as regards the results of pre-operative laboratory investigations with no statistically significant differences between both groups as regards hemoglobin level, platelet count, or INR level. And again, this balance in the baseline characteristics provides the basis for comparison between the study groups as it helps to minimize bias⁽³¹⁾.

The present study revealed that no statistically significant differences were found between both groups as regards the postoperative incidence of lower limb edema, major bleeding, wound infection, or GIT bleeding. On the other hand, a statistically significant difference ($p=0.018$) was found between both groups as regards the postoperative incidence of minor bleeding as it did not occur in 100% of the patients in the aspirin group and occurred in the form of ecchymosis in 25% of the patients in the rivaroxaban group. Nearly similar findings were published by *Anderson et al.*⁽³²⁾ who performed a similar study on 3424 patients (1804 undergoing total hip arthroplasty and 1620 undergoing total knee arthroplasty) aiming to compare the effects of aspirin with direct oral anticoagulants for prophylaxis against venous thromboembolism (proximal deep-vein thrombosis or pulmonary embolism) after total hip or total knee arthroplasty beyond hospital discharge. They found that no statistically significant differences were found between both groups as regards major or clinically relevant non-major bleeding complications. These findings are also comparable to those published by *Huang et al.*⁽³³⁾ who performed their study on 390 patients aiming to compare the efficacy and safety of aspirin with rivaroxaban following treatment with enoxaparin for prevention of VTE after hip fracture surgery. They found that no statistically significant differences were found between both groups as regards the rates of major bleeding events or clinically relevant non-major bleeding. And most recently, similar findings were also published by *Xu et al.*⁽³⁴⁾ who performed a meta-analysis which enrolled five studies with a total of 2257 patients in the aspirin

group and 2337 patients in the rivaroxaban group aiming to compare the efficacy of aspirin against rivaroxaban for the prevention of VTE following TKA and THA. They found that there were no differences between aspirin and rivaroxaban groups for either major bleeding, any bleeding, or wound complications.

And as regards the incidence of post-operative thromboembolism, the present study revealed that pulmonary embolism did not occur in any of the included patients and that DVT occurred in only 5% of patients in the rivaroxaban group. However, no statistically significant differences were found between both groups as regards the postoperative incidence of DVT or pulmonary embolism. Similar findings were published by *Anderson et al.*⁽³²⁾ as they reported no significant between-group differences in rates of thromboembolic events. And similarly, *Huang et al.*⁽³³⁾ reported no statistically significant differences between both groups as regards the incidence of pulmonary embolism. Recently, similar findings were published by *Xu et al.*⁽³⁴⁾ as they found that there were no differences between aspirin and rivaroxaban for either VTE or its components deep vein thrombosis and pulmonary embolism.

CONCLUSION

In this study, the incidence of DVT was found only 5% in the rivaroxaban group and 0% in the aspirin group. Aspirin can be considered a safe and effective agent in the prevention of VTE, and aspirin was not significantly different from the oral anticoagulant rivaroxaban for the prevention of DVT or pulmonary embolism after total knee arthroplasty.

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