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ORIGINAL ARTICLE

Comparison of the Results of Deep Venous Thrombosis Prophylaxis between Using Rivaroxaban or Aspirin Following Primary Total Hip and Knee Arthroplasties

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Background

Joint arthroplasty increases the risk of venous thromboembolism (VTE). VTE includes a wide scale of clinical presentations ranging from being asymptomatic, in most cases, to fatal pulmonary embolism. Both the American Academy of Orthopaedic Surgeons (AAOS) as well as the American College of Chest Physicians (ACCP) agree that routine prophylaxis must be used in all patients undergoing total hip and knee arthroplasties to lessen the risk of VTE. Pharmacological agents include aspirin, warfarin, low-molecular-weight heparins, factor Xa inhibitors, and direct thrombin inhibitors. Rivaroxaban is a direct factor Xa inhibitor and is currently recommended for use in VTE prophylaxis. Aspirin is an antiplatelet drug that prevent platelet aggregation and thrombus formation. Our study aimed to conclude if rivaroxaban and aspirin are both efficient to prevent VTE when given after primary total hip or knee replacement as a primary outcome and to measure the rate of complications that can occur following the administration of these drugs as a secondary outcome.

Patients and Methods

This prospective study was applied to 284 patients. Prior to surgery, all the patients were confirmed to get a free lower limbs venous Doppler with normal bleeding profile investigations. They were divided into two groups. The first group included 136 patients. Forty-four patients were prepared to have primary total hip replacement (THR), and 92 patients were prepared to have primary total knee replacement (TKR). The patients of this group were given a postoperative 10mg oral daily dose of rivaroxaban as a deep venous thrombosis (DVT) prophylaxis. The second group included 148 patients. Seventy-two patients were prepared to have primary THR and 76 patients were prepared to have primary TKR. The patients of this group were given a postoperative 81mg oral twice daily dose of aspirin. Rivaroxaban and aspirin were continued for 3 weeks for the TKR patients and 5 weeks for the THR patients. All patients were checked for risk of postoperative bleeding events and thrombotic complications. All the patients had new lower limbs venous Doppler study and bleeding profile investigations after termination of the anticoagulation therapy. At the end of follow-up period, at least 3 months, All the patients had new bleeding profile investigations.

Results

At the end of the follow-up period, all the patients in both groups were clinically free from VTE. In the rivaroxaban group, four (2.94%) patients had a silent DVT, which was discovered accidentally in the postoperative Doppler study, and the aspirin group, two (1.35%) patients had a silent DVT which was discovered accidentally in the postoperative Doppler study. In the rivaroxaban group, 18 (13.2%) patients had abnormal bleeding profile laboratory investigations (prothrombin activity <70%). Eight patients had no clinical manifestations, four patients had hemarthrosis, and six patients had severe bleeding. In the aspirin group, no patients complained of any bleeding complications or abnormal bleeding profile laboratory investigations.

Conclusions It is concluded that this study supported the previous series in the literature, which proved that both rivaroxaban and aspirin are highly effective in preventing VTE when used after hip and knee arthroplasties. They both have better patient compliance as they are taken through the oral route. However, aspirin has a lower cost and a lower risk of bleeding.

Keywords Arthroplasty, Aspirin, Bleeding, Rivaroxaban, Venous thromboembolism.
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INTRODUCTION

The total number of hip and knee arthroplasties is increasing every year all over the world. Joint arthroplasty increases the risk of venous thromboembolism (VTE). Without prophylaxis, 50% of patients having total hip replacement (THP) and 60% of patients having total knee replacement (TKR) will get VTE [1]. VTE includes a wide scale of clinical presentations ranging from being asymptomatic, in most cases, to fatal pulmonary embolism. If symptomatic, VTE has a higher possibility of readmission and prolonged hospitalization, more patient morbidity, decreased patient quality of life, and increased healthcare expenditures. In addition, pulmonary embolism is fatal without prophylaxis in 2% of cases [2–4]. Although hip and knee arthroplasties increase the risk of VTE, many other risk factors can cause more and more increases in the risk of postarthroplasty VTE. The National Institute for Health and Care Excellence (NICE) recognizes some of the risk factors for VTE, such as the previous history of VTE, age over 40 years, cancer (known or undiagnosed), varicose veins, obesity, vasculitis, chemotherapy, and acquired and inherited hypercoagulable states [5]. Other VTE risk factors include diabetes mellitus, hypertension (HTN), cardiac or chronic obstructive pulmonary disease patients, patients having a history of deep venous thrombosis (DVT) or pulmonary embolism, or having had prior surgery within the preceding 3 months [6]. Patients with a history of VTE have eight times more increasing risk of getting a new attack of VTE or pulmonary embolism during the high-risk period (e.g. following joint replacement surgery) compared with patients without a history of VTE [7]. Patients with such comorbidities have a more increased risk of VTE when having total hip or TKR with a more increased risk of being symptomatic. Both the American Academy of Orthopaedic Surgeons (AAOS) as well as the American College of Chest Physicians (ACCP) agree that routine prophylaxis must be used in all patients undergoing total hip and knee arthroplasties to lessen the risk of VTE [6]. VTE prophylaxis can be done by early mobilization and leg exercises, adequate hydration, mechanical methods for VTE prophylaxis such as anti-embolism stockings, intermittent pneumatic compression devices, and pharmacological agents for VTE prophylaxis or combination of methods according to the risk of occurrence of VTE. Pharmacological prophylaxis is nowadays considered the main corner of VTE prophylaxis despite the debate of which type to use to get the best protection against VTE with the least possibility of drug side effects. They include aspirin, warfarin, and low-molecular-weight heparins, such as enoxaparin, factor Xa inhibitors, and direct thrombin inhibitors [8]. Rivaroxaban is an oral anticoagulant and a direct factor Xa inhibitor. It is used for VTE prophylaxis. Aspirin is an antiplatelet drug that prevents platelet aggregation and prevents thrombus formation [8]. Routine monitoring for both rivaroxaban and aspirin is not recommended [8]. Our study aimed to conclude if rivaroxaban and aspirin are both efficient to prevent VTE when given after primary total hip or knee replacement as a primary outcome and to measure the rate of complications that can occur following the administration of these drugs as a secondary outcome.

PATIENTS AND METHODS

This prospective study was approved by the local ethical committee of our institution and has therefore been performed following the pertinent ethical guidelines (i.e. Declaration of Helsinki, as laid down in 1964 and revised in 2008). Written informed consent was obtained from all the patients. All the patients admitted to Al Hadra University Hospital during the period between February 2022 and December 2023 and prepared to have primary total hip or knee arthroplasty, where 348 patients were intended to be enrolled in our study. We excluded the patients with incomplete data from our study (preoperative and final follow-up clinical data, bleeding profile investigations, and lower limb Doppler venous study). Also, we excluded patients with a history of previous DVT, patients with bleeding profile abnormalities, patients who had any surgery during the last 3 months previous to the arthroplasty, patients with revision arthroplasties, and patients who cannot bear weight postsurgery. Sixty-four patients were excluded from our study. Two hundred eighty-four patients continued till the last follow-up, and all their data were available.

They were divided into two groups. The first group included 136 patients. The age range was from 24 to 72 years, with a mean age of 58.5. There were 80 females and 56 males. Forty-four patients were prepared to have primary THR and 92 patients were prepared to have primary TKR. One hundred twenty-six patients had

assisted weight bearing with a cam walker or crutches without having anticoagulation therapy. But, the other 10 patients were bed-ridden due to a fractured neck of the femur as they were prepared for THR and having (Clexane, 40,000IU, administered subcutaneously) as thromboembolism prophylaxis, continued as a daily dose, and stopped 24h preoperatively. The second group included 148 patients. The age range was from 21 to 80 years, with a mean age of 51.7. There were 100 females and 48 males. Seventy-two patients were prepared to have primary THR, and 76 patients were prepared to have primary TKR. One hundred thirty-two patients had assisted weight bearing with a cam walker or crutches without having anticoagulation therapy. But, the other 16 patients were bed-ridden due to a fractured neck of the femur as they were prepared for THR and having (Clexane, 40,000IU, administered subcutaneously) as thromboembolism prophylaxis, continued as a daily dose, and stopped 24h preoperatively. During preparation for surgery, history was taken from all the patients about comorbidities. None of them had a history of previous VTE or had surgery during the last 3 months previous to arthroplasty. All patients had Doppler study over the venous system of both lower limbs with bleeding profile investigations in conjunction with routine investigations needed for surgery. The surgeries for the patients with discovered VTE or those with abnormal laboratory investigations were postponed. All patients enrolled in our study had normal preoperative lower limbs and Doppler venous studies with normal bleeding profile investigations (PT, PTT, PA, INR). The anesthesia specialist was responsible for the decision on the appropriate anesthesia according to the general status of the patients. All the surgeries were performed in El-Hadra University Hospital by arthroplasty unit consultants. All surgeries were done without using a tourniquet. All wounds for THR and TKR surgeries were closed without using radivac. The need for intraoperative or postoperative blood transfusion was decided by anesthesia specialist according to intraoperative blood loss and postoperative complete blood count analysis (CBC). Postoperatively, adequate hydration was ensured for all the patients. The patients of the first group were given oral rivaroxaban 10mg as a thromboembolic prophylaxis daily dose, and the patients of the second group were given 81mg oral twice daily dose of aspirin. Both groups started treatment after 6h postoperatively. The vhoice of the drug was made randomly regardless of any factor that can affect the results of the study (age, type of surgery, comorbidities, etc.). After having radiographs to ensure the adequacy of arthroplasty, all the patients started a progressive physiotherapy program. Immediate postoperative exercises strengthen quadriceps muscles and improve the range of motion of the hip and knee joints. Partial weight bearing was allowed for all patients using a cam walker. Rivaroxaban and aspirin were continued for 3 weeks for the TKR patients and 5 weeks for the THR patients. In addition to patients monitoring for arthroplasty early success (stability, wound care, lack of infection, etc.), all patients were checked for risk of postoperative bleeding events and thrombotic complications. Bleeding complications included dressing soaking, hematoma, hemorrhage, acute postoperative blood loss anemia, hemarthrosis, and rates of blood transfusion during hospital stays and weekly follow-up visits. Thrombotic complications, including DVT, pulmonary embolism, stroke, and myocardial infarction were checked during weekly follow-up visits. After termination of the anticoagulation therapy (3 weeks for the TKR patients and 5 weeks for the TR patients), all our patients had new lower limbs venous Doppler study to check for VTE and new CBC and bleeding profile investigations to check for bleeding complications. All the patients were followed for at least 3 months postsurgery. At the end of follow-up period, all our patients had another new CBC and bleeding profile investigations to check for any delayed complications for the anticoagulation therapy and to check for the correction of the abnormalities that might occur with the patients after stoppage of the drugs.

Statistical Analysis

Data were analyzed by using SPSSR software (Statistical package for social science for personal computers' IBM, Armonk, New York, USA) using the Pearson χ^2 test and comparing means. Qualitative data were described using numbers and percentages. Quantitative data were expressed as mean±SD and *P* value less than 0.05 was considered significant.

RESULTS

After termination of the anticoagulation therapy either by rivaroxaban or aspirin (3 weeks for the TKR patients and 5 weeks for the THR patients), At the end of the follow-up period (at least 3 months), all the patients were found to be clinically free from VTE. In the rivaroxaban group, four (2.94%) patients had a silent DVT, which was discovered accidentally in the postoperative Doppler study, and in the aspirin group, two (1.35%) patients had a silent DVT, which was discovered also accidentally in the postoperative Doppler study. The six patients were sent for vascular surgery consultation. No patients had clinically manifested VTE or serious thrombotic complications such as pulmonary embolism, stroke, or myocardial infarction. There was an insignificant correlation between the use of rivaroxaban or aspirin and the prevention of DVT (Table 1).

After termination of the anticoagulation therapy, regarding the rivaroxaban group, 18 (13.2%) patients had abnormal bleeding profile laboratory investigations (prothrombin activity <70%). Eight patients had no clinical manifestations, four patients had mild hemarthrosis but

their CBC was within the accepted range, and six patients had bleeding (four patients from the surgical wound, two patients complained of nasal bleeding and melena) during the first 2 weeks postoperative. They complained of acute blood loss anemia and were readmitted for blood transfusion. Rivaroxaban was stopped for them and replaced by aspirin 81mg tablet twice daily. There was an insignificant correlation between bleeding complications and the use of rivaroxaban. Regarding the aspirin group, no patients complained of any bleeding complications or abnormal bleeding profile laboratory investigations. There was a significant correlation between the use of aspirin and the prevention of bleeding complications (P<0.001) (Table 2).

Regarding the rivaroxaban group, the four patients with silent DVT were females, had TKR, and were old age (their ages ranged between 62 and 68 years old), and all of them had multiple comorbidities. There was an insignificant correlation between thrombotic complications and comorbidities of the patients (Table 3).

Four patients with clinically manifested bleeding complications had a single comorbidity (HTN) and six patients suffered multiple comorbidities. There was an insignificant correlation between bleeding complications and comorbidities of the patients (Table 3).

Regarding the aspirin group, the two patients with silent DVT were also females, had THR, were old age (one patient was 64 years old and the other was 65 years old), and both had multiple comorbidities (HTN, diabetes mellitus). There was an insignificant correlation between thrombotic complications and comorbidities of the patient (Table 4).

At the end of follow-up period, at least 3 months, all the patients got new CBC and bleeding profile investigations. There were no late abnormalities discovered after the termination of the anticoagulation therapy, and all the abnormalities caused by the intake of the drugs were found to be corrected after the stoppage of the treatment (100%) at the final follow-up.

Table 1: Thrombotic complications at the end of follow-up:

Thrombotic complications	Rivaroxaban group	Aspirin group
DVT	4(2.94)	2(1.35)
PE	0	0
MI	0	0
Stroke	0	0

DVT: Deep venous thrombosis; MI: Myocardial infarction; PE: Pulmonary embolism.

Table 2: Bleeding complications at the end of follow-up:

Bleeding complications	Rivaroxaban group	Aspirin group
Abnormal laboratory investigations	18(13.2)	0
No clinical symptoms	8	0
Bleeding	6	0
Hemarthrosis	4	0
Acute blood loss anemia	6	0
Late need for transfusion	6	0

Table 3: Correlation between comorbidities and complications for the rivaroxaban group:

Comorbidities	Number of patients	Thrombosis complications	Clinically manifested bleeding complications
No comorbidity	56(41)	0	0
Single comorbidity	60(44)	0	4
Multiple comorbidities	20(15)	4	6
Total	136(100)	4(2.94)	10(7.35)

Table 4: Correlation between comorbidities and complications for the aspirin group:

Comorbidities	Number of patients	Thrombosis complications	Clinically manifested bleeding complications
No comorbidity	54(36.5)	0	0
Single comorbidity	58(39.2)	0	0
Multiple comorbidities	36(24.3)	2	0
Total	148(100)	2(1.35)	0

DISCUSSION

There is no doubt that total hip and total knee arthroplasty increase the risk of occurrence of VTE, which has multiple presentations ranging from being silent to fatal pulmonary embolism. So, postarthroplasty prophylaxis against VTE is a must. This is agreed upon by both the American Academy of Orthopaedic Surgeons (AAOS) and the American College of Chest Physicians (ACCP) [6]. Pharmacological agents became the cornerstone in the management of VTE. The optimal pharmacological agent has to meet the following criteria: high efficacy in preventing VTE, minimal risk of bleeding, cost-effectiveness, ease of administration, and associated with decreased postoperative complications. Many factors can be interpreted with the effectiveness and the side effects of the drugs, some related to the drug itself and some related to the associated comorbidities, which differ from one patient to another. So, there continues to be controversy

regarding the optimal agent for prophylaxis against VTE after total joint arthroplasty [9].

Rivaroxaban is an oral anticoagulant and is a direct factor Xa inhibitor that interrupts the coagulation cascade and the development of thrombi. It is rapidly absorbed in the stomach and small intestine and peak serum levels occur in 2–4h following administration. It has a half-life of 5–13h [8]. Aspirin is an antiplatelet drug that prevents platelet aggregation and prevents thrombus formation [8].

In our study, we tried to discuss the efficacy of rivaroxaban and aspirin in prophylaxis against VTE when given after primary total hip or knee replacement as a primary outcome and to measure the rate of complications such as bleeding, need for blood transfusion as a secondary outcome. As regards our primary outcome, all the patients were clinically free from VTE. Four (2.94%) patients of the rivaroxaban group and two (1.35%) patients of the aspirin group had a silent DVT, which was discovered accidentally in the postoperative Doppler study. There was an insignificant correlation between the use of rivaroxaban or aspirin and the protection against VTE. Our results were slightly different from the results discovered by Ning *et al*., [10] and Stewart [11] and this may be attributed to the small number of studied cases in our study when compared with other studies. Some studies compared the efficacy of rivaroxaban versus aspirin and enoxaparin in the prevention of VTE, such as Eriksson *et al*., [12] and Lassen *et al*., [13]. They found that both give nearly the same percentage of protection.

As regards our secondary outcome, in the rivaroxaban group, 18 (13.2%) patients had abnormal bleeding profile laboratory investigations (prothrombin activity <70%). Eight patients had no clinical manifestations, four patients had mild hemarthrosis, and six patients had severe bleeding during the first 2 weeks postoperative. They complained of acute blood loss anemia and were readmitted for blood transfusion. There was an insignificant correlation between bleeding complications and the use of rivaroxaban. Similar results were found by Wood *et al*., [14].

Regarding the aspirin group, no patients complained of any bleeding complications or abnormal bleeding profile laboratory investigations. There was a significant correlation between the use of aspirin and the prevention of bleeding complications (<0.001). Some studies compared the complications of the use of rivaroxaban, enoxaparin, and aspirin, such as Zou *et al*., [15] and Lindquist *et al*., [16]. They found that the rate of complications is quite similar between rivaroxaban and enoxaparin, but also, the rate of complications was much decreased with the use of aspirin.

Rivaroxaban and aspirin are given through the oral route, unlike enoxaparin, which is given by injection. Enoxaparin has a higher cost than rivaroxaban and aspirin. Aspirin also has a lower cost and a lower complication rate when compared with rivaroxaban itself which means better patient compliance. We recommend beginning anticoagulation therapy either by rivaroxaban or aspirin after 6h postoperatively.

All the patients who were presented with complications in our study either silent or manifested complications (four patients with silent VTE, 18 patients with abnormal bleeding profile of the rivaroxaban group, and the two patients who had silent VTE in the aspirin group), all of them suffered from comorbidities. There was an insignificant correlation between thrombotic or bleeding complications and comorbidities of the patients for both groups. But, this means that patients with multiple comorbidities may need to have more close observation and monitoring of the patients.

We used postoperative Doppler ultrasound to detect postoperative VTE. It is operator-dependent, with many false results and costly procedures when ordered for all the patients after surgery. Many studies have mentioned that it does not have as much benefit to be used as a routine after surgery [17].

In this study, we had some limitations. The small number of studied patients as our study was a prospective study with the need for preoperative and postoperative laboratory investigations and a Doppler study, which was difficult to do for many patients. Also, detecting postoperative VTE by Doppler study is operator-dependent and it needs high experience from the radiology specialist, which may give false results. The dose of rivaroxaban and aspirin given to all the patients was a fixed dose regardless of the associated comorbidities or the weight of the patients and without monitoring of the blood drug level, which may be needed to get the best dose that gives the best results with the least complications.

CONCLUSION

Rivaroxaban and aspirin are highly effective in preventing VTE when used after hip and knee arthroplasties with better patient compliance when taken through the oral route. They both have better patient compliance as they are taken through the oral route. But, aspirin has a lower cost with a lower risk of bleeding and this supports the previous series in the literature.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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