

SAFETY OF RIVAROXABAN FOR PROPHYLAXIS VEIN THROMBOSIS POST TOTAL HIP AND KNEE REPLACEMENT

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ABSTRACT

Orthopaedic surgery such as surgery on the pelvis and knee bones has a high risk of developing Deep Vein Thromboembolism (DVT), especially in patients with hypercoagulability. Venous thromboembolism is the main cause of morbidity and mortality in orthopedic patients that can be prevented using thromboprophylaxis, but on the other hand is related to the risk of bleeding side effects. The study aimed to evaluate the safety of oral Rivaroxaban prophylaxis in patients after Total Hip and Knee Replacement. This research applied cross sectional technique. Retrospective data were taken from the medical records of Dr. Moewardi Surakarta, period January 2023- July 2024. The data taken are secondary data from the patient's medical record by recording clinical symptoms that appear. Rivaroxaban safety evaluation includes the incidence rate of bleeding as well as the factors that influence the occurrence of bleeding. A total of 38 patients met the inclusion criteria of the study. Bleeding occurred in 4 cases (10.5%). Factors that affect the incidence of bleeding renal failure ($p = 0.001$). Monitoring of Rivaroxaban side effects is indispensable. Pharmaceuticals can play an important role in monitoring and preventing the occurrence of bleeding by paying attention to risk factors, especially kidney failure.

KEYWORDS

bleeding; total hip and knee replacement; rivaroxaban



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INTRODUCTION

According to who (World Health Organization), osteoarthritis (OA) is a long-term chronic disease characterized by joint cartilage damage that causes bones to rub against each other and gives rise to stiffness, pain and impaired movement. Osteoarthritis most commonly occurs in the lower joints, hands, feet, and spine and can occur in the shoulders and hips (who, 2013).

According to the United Nations (UN), by 2050 more than 20% of people over the age of 60 will have OA, with 15% having OA symptoms and a third with severe disability. The prevalence of knee OA in Indonesia is quite high, reaching 15.5% in men and 12.7% in women. It is estimated that 1-2 million elderly people in Indonesia suffer from disabilities due to OA (Soeroso, 2009).

Osteoarthritis can be caused by several factors, namely factors that can be modified (obesity, occupational injury, dietary factors and physical activity) and cannot be modified (age, genetics and gender)(Plotnikoff et al., 2015).

Based on the consensus on the management of knee and hip OA by Osteoarthritis Research Society International (OARSI), there are two therapeutic modalities, namely non-surgical and surgical therapy. Initial management of knee OA is conservative therapy, but if symptoms persist surgical therapy may be considered. Surgical therapy options that can be done are arthroscopic debridement, cartilage repair surgery, osteotomy with axis-correction, and unicompartmental or total knee arthroplasty (TKA)(Rönn, Reischl, Gautier, & Jacobi, 2011).

In cases of progressive joint instability, surgical treatment is indicated. Total Knee Arthroplasty (TKA) is the most effective treatment for advanced knee OA that affects more than one compartment and fails conservative therapy (Rönn et al., 2011). The main reasons for readmission in TKA patients are limited movement, complications from wounds, surgical wound infections, bleeding, and venous thromboembolism (TEV) (Mulcahy & Chew, 2014). Venous thromboembolism (TEV) is a major cause of morbidity and mortality in orthopedic patients, one of the TEV disorders is deep vein thrombosis (TVD) (Rachidi et al., 2013). The most dangerous complication of TVD is pulmonary embolism (PE) which can cause death. More than 30% of patients can experience repeated TVDs within 8 years after diagnosis. Repeated TVD can cause PE and venous valve damage, chronic venous insufficiency, and require long-term management(Samare Fekri, Khalily Zade, & Fatehi, 2014).

All patients undergoing joint replacement are at risk of DVT due to the duration of surgery and reduced perioperative mobility. To reduce the risk of DVT, almost all patients receive treatment for up to 35 days of anticoagulant after surgery(Anderson et al., 2018).

Rivaroxaban is used orally, directly, reversibly and as a selective factor Xa inhibitor, in both free and prothrombin-bound forms. The advantages of rivaroxaban are predictable pharmacokinetics and pharmacodynamics, cheaper prices, fewer interactions between drugs, fixed doses, does not require periodic laboratory supervision, high bioavailability, can inhibit free, bound and clot prothrombinase related to factor Xa without having a direct effect on platelet aggregation, is not influenced by age, sex and weight, and is not influenced by race(Mueck, Schwes, & Stampfuss, 2013), but anticoagulants have a risk of bleeding disorders so they need to be of special concern(Kjerpeseth et al., 2019).

Bleeding that occurs can be major or minor including intracranial, gastrointestinal and other bleeding(Kjerpeseth et al., 2019). Research conducted by Wang et al., (2019) showed that patients with NOAC (novel oral anticoagulant) administration had a lower incidence of major bleeding and gastrointestinal tract bleeding than warfarin. According to Paciaroni et al., treatment with NOAC has a 5% increase in major bleeding events. Bleeding rate in patients receiving dabigatran (0.5%), rivaroxaban (2.5%), and apixaban (2.9%)(Paciaroni et al., 2017). Elderly patients, renal failure, anemia, alcohol, hypertension, cancer, genetic factors and the occurrence of stroke can increase the risk of bleeding(Senoo, Lane, & Lip, 2014). Female gender and NSAID exposure are considerations for assessing bleeding risk. In addition, the use of anticoagulants is a major risk factor for bleeding(Piel-Julian et al., 2018).

The purpose of the study was to evaluate the safety of Rivaroxaban therapy in post-Total and Hip Replacement patients. The benefits in this study are as information in determining the monitoring of the use of anticoagulant drugs in hospitals.

RESEARCH METHOD

The study used a cross-sectional research design. This research was conducted in January 2023- July 2024. The research has been approved by the health research ethics commission of RSUD Dr. Moewardi Surakarta Number : 1.911 / VII/HREC / 2024.

All patients suffering from OA who underwent Total Hip and Knee Replacement at RSUD Dr. Moewardi Surakarta which met the inclusion and exclusion criteria was included in the research subject. The inclusion criteria in this study were patients who had been diagnosed with OA by doctors undergoing Total Hip and Knee Replacement with oral rivaroxaban prophylaxis, while the exclusion criteria were patients who had a history of blood or heart disorders, such as: blood coagulation disorders, atrial fibrillation, valve abnormalities, stroke and others.

Safety evaluation includes the occurrence of bleeding during hospitalization. Information is obtained through medical record records. Major bleeding was defined as overt bleeding with any of the following: decrease in Hb (hemoglobin) of at least 2 g/dL and bleeding that requires red blood cell transfusion of 2 or more, for example bleeding in the gastrointestinal tract, gum area, hematemesis and hematuria (Schulman & Kearon, 2005).

RESULTS AND DISCUSSION

Table 1 shows the distribution of post-Total Hip and Knee Replacement patients who received Rivaroxaban at Dr. Moewardi, Surakarta by age, the highest age group was 60-74 years old (elderly age) with 22 samples (73.3%). The lowest age group was 75-90 years old (old age) with 1 sample (3.3%). Based on the results of the study showed that OA patients based on age, the highest was the group of women aged 60-74 years (elderly age) 73.3%, in accordance with the research of Rahmadiyah et al., stating that 43.75% of OA occurred in elderly women (>60 years) (Hillarp et al., 2011).

The majority of age groups that experience the incidence of osteoarthritis are the age group of 60-74 years (elderly age) as much as 73.3%. This study is in accordance with the 2013 WHO journal, which estimates that 10-15% of the population aged >60 years will experience OA, and the research of Chin Teck NG et al., in 2013 stated that as many as 12.1% of American citizens >60 years experience OA symptoms as evidenced by radiological examination (Falck-Ytter et al., 2012).

Table 1. Characteristics of patients after Total Hip and Knee Replacement who received Rivaroxaban at Dr. Moewardi, Surakarta.

Characteristics	Number (percentage)
Age	
45-59 years old (<i>middle age</i>)	7 (18.4%)
60-74 years old (<i>elderly age</i>)	30 (78.9%)
75-90 years old (<i>old age</i>)	1 (2.6%)
Gender	
Male	16 (42.1%)
Female	22 (57.9%)
Comorbidities	
It is not.	16 (42.1%)
Chronic Kidney Disease	7 (18.4%)
Cardiovascular	10 (26.3%)
Cancer	4 (10.5%)
Diabetes Mellitus	1 (2.6%)
Antiplatelet Use	
Yes	2 (5.3%)

No	36 (94.7%)
Smoking Behavior	
Yes	8 (21.1%)
No	30 (78.9%)

Age is the strongest risk factor for the onset of OA, related to the combination of changes in the capacity of joint tissue to adapt to biomechanical stress. Increased prevalence and incidence of age-related OA is a consequence of cumulative exposure to various risk factors and biological changes that occur in aging, the aging process can result in weakness around the joints, such as cartilage thinning, weakened muscle strength, poor proprioception and oxidative damage(Heidari, 2011).

The results of this study showed that the incidence of TVD in osteoarthritis patients was higher in women (76.7%) than in men (23.3%). In accordance with the research of Sonjaya et al., which states that the incidence of OA is higher in women (82.54%) than in men (18.59%). Thus, this it is also not much different from Litwic's research et al., stating that OA is more common in women than men, with a ratio of 4:1(Litwic, Edwards, Dennison, & Cooper, 2013).

Women, in addition to experiencing OA more often than men, tend to experience heavier OA. This difference is related to the timing of menopause, the decrease or loss of estrogen at menopause increases a woman's risk of developing OA(Linn, Murtaugh, & Casey, 2012). Estrogens have protective and detrimental effects on articular cartilage

The most common comorbid was cardiovascular in 10 patients (26.3%) followed by renal failure in 7 patients (18.4%) and DM in 1 patient (2.6%). The results of this study are in line with the results of Shorr et al., (2012) stating that kidney disease including chronic kidney disease (CKD) as a risk factor for VTE. Several CV risk factors among 1.1 million participants in 76 groups found that older age, smoking, higher levels of adiposity, and lower alcohol consumption were associated with a higher risk of DVT(Wang, Rosendaal, Cushman, & van Hylckama Vlieg, 2022). The study found CKD3B to be a risk factor for patients receiving enoxaparin as thromboprophylaxis, compared to milder CKD, for example. CKD1, CKD2 or CKD3A. In addition, the researchers of the above paper have also considered "CKD3B" as a potential risk factor. Increased blood pressure levels around 60-80% are at risk of thromboembolism and bleeding(Cools et al., 2021).

Bleeding side effects occurred in 4 patients (10.5%) in table II. In this study, the number of subjects using DOAC-type anticoagulants is very limited, so further research is needed in other hospitals with a larger number of subjects to get a more accurate picture of side effects. The limited time of the study was the reason why the research was not conducted in a multicenter manner.

Antiplatelet therapy should be considered against the risk of bleeding(Dong, Wang, & Sundararajan, 2020). Another study by So and Eckman mentions the combination of antiplatelet and anticoagulant therapy in atrial fibrillation patients can reduce the incidence of stroke-associated atrial fibrillation or CV events and cause an increase in major bleeding(So & Eckman, 2017).

Table 2. The effect of anticoagulant use on patients after Total Hip and Knee Replacement who received Rivaroxaban at Dr. Moewardi, Surakarta.

Outcome	Number (percentage) 38
Total bleeding	
This is not happening.	34 (89.5%)
Bleeding	4 (10.5%)
Major Bleeding	3 (75%)
Minor Bleeding	1 (25%)

The incidence of bleeding in the use of Rivaroxaban is 10.5%. These results are in line with the study conducted by Yasaka et al., 11 patients after administering rivaroxaban experienced major bleeding side effects (Yasaka et al., 2019). The time of major bleeding ranged from < 3 days to 14 days after rivaroxaban administration. A prospective Observational Study in Rome, Italy after three months of treatment with Edoxaban in ischemic stroke patients reported two major gastrointestinal bleeding and 11 minor bleeding (Frisullo et al., 2020).

Major types of bleeding that occur include melena and hematuria as a result of the use of Rivaroxaban after Total Hip and Knee Replacement. There were 2 patients who experienced melena bleeding and 1 patient experienced hematuria. In an observational study in Iran, the incidence of gastrointestinal bleeding was significant in the rivaroxaban group by 34% while warfarin was 61% ($p = 0.001$). Melena is a type of gastrointestinal bleeding that occurs in both groups. The type of minor bleeding that occurs is ecchymosis.

Renal failure and the use of antiplatelet are variables that have a relationship with safety (bleeding incidence) in the hospital after bivariate analysis. This can be seen with a significant value < 0.05 . Patients with concomitant renal failure have a higher risk of bleeding events compared to patients without concomitant renal failure. The factors that affect bleeding in this study can be seen in table III. The results of this study have similarities with research conducted by Dahal et al., patients with CKD, the use of warfarin has an effect in increasing the risk of major bleeding (RR 1.30; 95% CI 1.08-1.56; $P = 0.005$) (Dahal, Kunwar, Rijal, Schulman, & Lee, 2016). Research is in line with research 66 that the addition of antiplatelet agents to warfarin can increase the risk of life-threatening and major bleeding events. In another study, the incidence of bleeding increased from 1.3% in single warfarin use to 1.9% in antiplatelet warfarin use (Shireman, Howard, Kresowik, & Gami, 2005).

Table 3. Factors affecting bleeding events in patients after Total Hip and Knee Replacement who received Rivaroxaban at RSUD Dr. Moewardi, Surakarta.

Factor	p-value
Age	449
Gender	0.477
Chronic Kidney Disease	0.001
Cardiovascular	0.144
Cancer	0.769
Diabetes Mellitus	0.941
Smoking Behavior	0.762
Antiplatelet Use	0.000

CONCLUSION

There were 4 cases of bleeding in patients after Total Hip and Knee Replacement who received Rivaroxaban at Dr. Moewardi, Surakarta. Monitoring of side effects using Rivaroxaban becomes indispensable. Pharmaceuticals can play an important role in monitoring and preventing bleeding events by paying attention to risk factors in patients, especially kidney failure.

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