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Original Article

Efficacy and safety of rivaroxaban in preventing deep venous thromboembolism after major orthopedic operations

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Abstract: The study aims to evaluate the efficacy and safety of rivaroxaban in comparison with enoxaparin in preventing deep venous thromboembolism (VTE) after major orthopedic surgery. In this study, 268 patients were enrolled and underwent major orthopedic surgeries between October 2011 and July 2014. Of the 268 patients, 135 received oral rivaroxaban and 133 received enoxaparin via hypodermic injection. Postoperative complications were compared between the rivaroxaban and enoxaparin groups. The primary end points included VTE, complications, readmission rate, severe and moderate bleeding events, and death. No significant differences in the incidence of VTE, blood transfusion amount, and readmission rate were observed between the rivaroxaban and enoxaparin groups. The secondary bleeding rates were 2.2% and 6.0% in the rivaroxaban and enoxaparin groups, respectively. The wound complication rates were 3.0% and 6.8%, respectively. None of the patients in either group experienced pulmonary embolism, severe bleeding, or death. No significant differences in the incidence rates of VTE and severe bleeding were observed between the two groups. However, rivaroxaban was safer than enoxaparin with regard to secondary bleeding and complications.

Keywords: Arthroplasty, hip joint, knee joint, hip fracture, venous thrombosis, rivaroxaban, enoxaparin

Introduction

Total hip replacement (THR), total knee replacement (TKR), and hip fracture surgery (HFS) are high risk factors for venous thromboembolism (VTE). In particular, deep venous thromboembolism (DVT) is caused by vascular endothelial injury, slow blood flow, and hematic hypercoagulative state. The incidence rates of VTE and pulmonary embolism (PE) without any preventive measures were 40-60% and 0.1%-0.2%, respectively [1, 2]. The incidence rates of fatal PE were 0.1%-0.2% (THR), 0.2%-0.7% (TKR), and 3.6%-12.9% (HFS), respectively. Such high incidences and severely adverse consequences have caught the attention of an increasing number of researchers. Identification of measures to effectively and safely reduce the incidences of VTE and PE has gained increasing attention. Recently, national clinical research guidelines indicated that orthopedists should administer anticoagulant therapy after major orthopedic surgery.

Meanwhile, Chinese guidelines for prevention and treatment of VTE and PE introduced several measures to follow after a major orthopedic surgery [3], including 1) general prevention: careful surgical manipulation, prevention of vein intimal injury, use of a tourniquet as standard procedure, elevation of the injured limb to prevent venous return obstruction, encouraging patients to turn, and accurate increase in fluid infusion; 2) application of plantar vein pump and intermittent pneumatic compression, and use of stretch socks with pressure gradients; 3) prophylactic medications.

Many studies have demonstrated that medications could prevent the occurrence of VTE after major orthopedic surgery [1-6]. Common medications include low-molecular-weight heparin, factor Xa inhibitor, and warfarin. However, low-molecular-weight heparin requires hypodermic injection, which limits its use in patients with low compliance. Meanwhile, warfarin therapy also has some disadvantages: for example, the

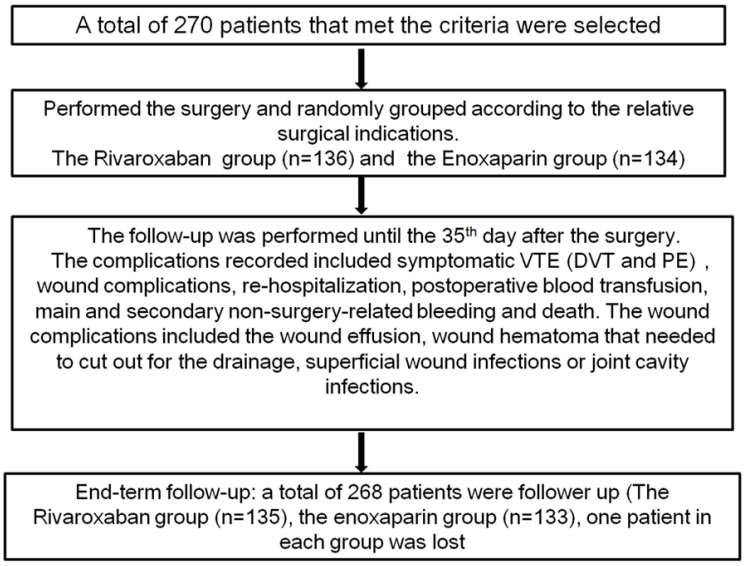

Figure 1. The flow chart for patients' recruitment. Note: Inclusion and exclusion criteria. The inclusion criteria included hip-knee osteoarthritis or rheumatoid arthritis, peri-hip fracture-caused total hip replacement or internal fixation. The exclusion criteria included the patients that were elderly, combined with many complications, could not tolerate the surgery, with known hypercoagulable state, with active bleeding or bleeding trend, with obvious liver diseases (such as acute hepatitis, chronic active hepatitis, cirrhosis), with coagulation disorder before or after the surgery and perioperative infections.

concentration of warfarin needs to be monitored.

Rivaroxaban, an oral medication, is a direct inhibitor of factor Xa [7-9] and demonstrates higher compliance among patients compared with low-molecular-weight heparin [10]. Approved for domestic sale in 2009, rivaroxaban could highly selectively and competitively inhibit the activities of free and bound factor Xa and prothrombin, and prolong partial activated thromboplastin and prothrombin times in a dose-dependent manner. Rivaroxaban is unable to inhibit thrombin (activated factor II), has not been proven to influence platelets, and possesses a low bleeding risk and wide safety margins. Rivaroxaban is the world's first oral anticoagulant; the dose is fixed, it needs no clinical monitoring, produces little interaction with food and other drugs, does not require coagulation tests, and the clinical application is very convenient. Based on numerous clinical studies, rivaroxaban was approved for use in Britain to prevent DVT after THR and TKR [1]. The present study aimed to assess and compare the efficacy and safety of use between rivaroxaban and enoxaparin in preventing deep VTE after major orthopedic surgery, and to determine a safe and effective anticoagulation method.

Materials and methods

General data

From October 2011 to July 2014, 270 patients underwent major orthopedic surgeries in our hospital (268 patients were followed up, **Figure 1**). The power analysis was calculated as follows: P_0=0.02, P_1=0.05, α=0.05, m=133/135=0.99, n=135. The study consisted of 135 rivaroxaban subjects (case) and 133 enoxaparin subjects (control). Prior data indicated that the probability of exposure among controls is 0.02. If the true probability of exposure among cases is 0.05, the null hypothesis that the exposure rates for case and controls are equal with probability (power) 0.268 will be rejected. The Type I error probability associated with the test of this null hypothesis was 0.05. We used an uncorrected chi-squared statistic to evaluate this null hypothesis.

In total knee arthroplasty (TKA), the knee prosthesis was implanted via the anterior knee median incision, as well as the medial patellar approach, after complete exposure and the osteotomy was performed, and the bone cement and prosthesis were placed. In total hip arthroplasty (THA), the lateral approach was used to separate the gluteus maximus, the partial external rotators was exposed and cut off, the joint capsule was cut, the osteotomy was performed, and the prosthesis was placed. The surgical method was adopted according to the specific fracture type around the hip, since TKA and THA were operated by the same group, so the procedures were similar, and the intraoperative medicine. The inclusion criteria included hip-knee osteoarthritis or rheumatoid arthritis, peri-hip fracture-caused total hip replacement or internal fixation. The exclusion criteria included the patients that were elderly, those who showed multiple complications, could not toler-

Table 1. Comparison of general data between patients with rivaroxaban and enoxaparin

Variables	Rivaroxaban group (n=135)	Enoxaparin group (n=133)	*P or t* value*
Sex (M/F)	58/77	51/82	0.398*
Age (Y)	72.7±8.5	69.9±10.4	2.494
BIM (kg/m^2)	27.8±6.1	26.6±5.5	1.837*
Diabetes (No.)	14 (10.3%)	15 (11.3%)	0.828*
Hypertension (N)	77 (57.0%)	69 (51.9%)	0.397*
Coronary heart disease (N)	18 (13.3%)	16 (12.0%)	0.749*
Lung disease (N)	13 (9.6%)	9 (6.8%)	0.393*
Cerebrovascular disease (N)	13 (9.6%)	11 (8.3%)	0.697*

*P value > 0.05 was regard as no statistically significant differences in sex, body mass index, and complications were observed between the rivaroxaban and enoxaparin groups.

Table 2. Comparison of Postoperative complications between patients with rivaroxaban and enoxaparin

Variables	Rivaroxaban group (n=135)	Enoxaparin group (n=133)	χ^2 value*
VTE	2 (1.5%)	3 (2.3%)	< 0.001
Blood transfusion	10 (7.4%)	11 (8.3%)	0.001
Secondary bleeding	3 (2.2%)	8 (6.0%)	2.442
Re-admission	4 (3.0%)	6 (4.5%)	0.119
Wound complications	4 (3.0%)	9 (6.8%)	2.093
Slight effusion	1 (0.7%)	2 (1.5%)	< 0.001
Hematoma	3 (2.2%)	3 (2.3%)	< 0.001
Superficial infection	0	2 (1.5%)	0.245
Joint cavity infection	0	2 (1.5%)	0.245
Second operation	3 (2.2%)	5 (3.8%)	0.144

*P value < 0.05 was regard as statistically significant.

ate the surgery, with known hypercoagulable state, with active bleeding or bleeding trend, with obvious liver diseases (such as acute hepatitis, chronic active hepatitis, cirrhosis), with coagulation disorder before or after the surgery and perioperative infections. All patients were divided randomly into the rivaroxaban group and the enoxaparin group. There was no obvious coagulant function abnormality in the two groups, and the values of TT, PT-INR, APTT and PT are within the normal range. No statistically significant differences in sex, body mass index, and complications were observed between the rivaroxaban and enoxaparin groups, but the age difference between both groups was statistically significant (**Table 1**). This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Tianjin Medical University. Written informed consent was obtained from all participants.

Methods

Rivaroxaban group: 10 mg of oral rivaroxaban was administered daily starting 12 h after the surgery to 35 days after the surgery. Enoxaparin group: 40 mg of enoxaparin was injected daily starting 12 h after the surgery until the day of hospital discharge. Follow-up was performed until 35 days after the surgery. VTE (DVT and PE) and wound complications, hospital readmissions, postoperative blood transfusions, primary and secondary bleeding, death, and other complications unrelated to surgery, were seen. Wound complications included oozing, wound hematomas, superficial wound infections, or joint cavity infections.

Statistical analysis

Statistical analysis was performed using the SPSS (Statistical Package for the Social Sciences) 13.0 software. The numerical data were expressed as mean ± SD ($\bar{x}$ ± s). The intergroup comparison of numerical data was performed using the student's *t* test, and the comparison of counting data was performed using the chi-square test (χ^2 test). A $P < 0.05$ denoted a significant statistical difference.

Results

No patient in either group experienced severe bleeding or death. Furthermore, no statistically significant differences in the incidence of VTE, the ratio of postoperative retransfusion, and readmission rate, were observed between either group. Symptomatic DVT was confirmed through color Doppler ultrasonography in 2 patients from the rivaroxaban group and in 3 from the enoxaparin group. However, none of the patients in either group developed PE. No statistically significant differences in secondary bleeding events and complications were

observed between groups. Secondary bleeding events that occurred included endoscopically confirmed upper gastrointestinal bleeding without blood transfusion therapy. Joint cavity infection, which was positive in one THA case and negative in another TKA case, based on bacterial cultures of wound secretion, and superficial would infection occurred in the enoxaparin group, but not in the rivaroxaban group. All patients who developed infectious complications were treated with antibiotics, and wound dressings were replaced regularly. In the rivaroxaban group, 2 THA patients and 1 TKA patient developed wound hematomas. In the enoxaparin group, 1 TKA and 2 HFS patients developed wound hematomas. For these patients, anticoagulant therapy was discontinued and hematoma evacuation was performed (**Table 2**).

Discussion

Venous thromboembolism is a common clinical syndrome among vascular diseases. This includes deep venous thrombosis and pulmonary thromboembolism. Increased blood viscosity, slow blood flow, and vessel wall damage-which occur in post-operative patients and those bedridden due to chronic disease and limb disorders-are the main reasons. Because of the long-term limb braking time after the hip orthopedic surgeries, joint flexion during surgeries, compression from tourniquet use, and postoperative long-term bed rest, venous blood flow velocity is slowed down. Surgical trauma and traction may lead to venous intimal injuries, and various other reasons caused by orthopedic hip surgery increase the incidence of postoperative deep venous thrombosis. Pulmonary embolism, occurring secondarily to proximal deep venous thrombosis, becomes the main reason for unexpected death after orthopedic surgery.

Foreign and domestic scholars have been actively searching for one effective method to decrease the incidence of deep venous thrombosis, and, thereby, reduce the morbidity and fatality rate secondary to pulmonary embolism. After extensive prophylactic measures, pharmacological methods would be the most logical step in preventing deep venous thrombosis occurring after orthopedic surgery [11, 12].

This study demonstrated no obvious difference in the incidence of VTE or of severe bleeding between the rivaroxaban and enoxaparin groups. Rivaroxaban was an effective oral anticoagulant. The question of whether rivaroxaban increases bleeding rate, or delayed wound healing, or whether it is associated with potential infection of the joint cavity has widely gained attention. Jensen et al. [13] has performed a retrospective cohort study and reported that the incidence rate of wound complications was lower in the rivaroxaban group (1.8%) than in the tinzaparin group (3.94%). Moreover, a statistically significant difference in wound complications was observed between the rivaroxaban group (n=559 consecutive patients) and the tinzaparin group (n=489 consecutive patients). Generally, patients with wound complications need secondary surgery to clear hematomas. In this study, no significant differences in the postoperative incidence rate of deep VTE and of secondary blood transfusion were observed between the rivaroxaban and enoxaparin groups, indicating that both medications had reliable efficacy. In addition, no massive hemorrhagic event occurred in both groups. Furthermore, the incidence rates of wound complications were 3.0% and 6.8% in the rivaroxaban and enoxaparin groups, respectively, and the secondary surgical rates were 2.2% and 3.8%, respectively. The differences were not statistically significant. These results differ from those of previous studies and thus need further confirmation.

Symptomatic VTE requires a relatively long treatment time, but its incidence rate is low. A meta-analysis of rivaroxaban for thromboprophylaxis implied that the incidence rate of VTE was 1% in the enoxaparin group and 0.5% in the rivaroxaban group [14]. Postoperative wound complications of THA and TKA mainly presented with wound hematomas and increased infection rate. The incidences of wound hematomas and infection reportedly required surgical intervention in about 1-2% of cases. Management of joint infection, which involves meticulous washing of the wound, presents a potential psychological and physiological harm to the patient, and could lead to added hospital expenses, prolonged hospital stay, more acute deformity, and mortality. Wound complications undermine the otherwise benefit of the low incidence of DVT. In order to balance the risks and benefits, these safety concerns should be addressed. Moreover, the convenience of using oral factor Xa inhibitors

could improve patient compliance, and provide a better anticoagulant therapy option for patients in clinical settings [15-20].

Recently, the RECORD study indicated that rivaroxaban, as the first approved oral inhibitor of factor Xa, has shown positive effects, especially on hip replacement and knee replacement patients. Animal experimentation has proved that rivaroxaban could inhibit factor Xa and prothrombin complex concentrates selectively, competitively, and reversibly, without increasing bleeding time. With its high bioavailability, efficacy, and safety, rivaroxaban performed much better than conventional anticoagulants without significantly increasing the risk of severe bleeding [21-23]. Based on these large-scale and randomized studies, we suggest rivaroxaban as a replacement for enoxaparin in the prevention of VTE [7]. The sample size of this study was relatively small, the follow-up time was relatively short, and these limitations need to be addressed in further studies.

Conclusion

In summary, the effectiveness and safety of rivaroxaban in preventing the formation of deep vein thrombosis after major orthopedic surgery were clear. As the first licensed oral factor Xa inhibitor, rivaroxaban provides more options for the pharmacologic prevention of deep venous thrombosis after major orthopedic surgery. A full-course drug therapy resulting from increased patient compliance, and the drug's relative safety, not only produced definitive effects that could significantly reduce the incidence of deep vein thrombosis after major orthopedic surgery, but also merit further study and investigation.

Disclosure of conflict of interest

None.

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