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Rivaroxaban vs. enoxaparin for preventing venous thromboembolism after hip fracture operations: a retrospective cohort study

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Introduction: Emerging evidence suggests that rivaroxaban may be effective in preventing venous thromboembolism (VTE) in patients with orthopedic trauma, resulting in fewer bleeding complications. This study aimed to evaluate the efficacy and safety of rivaroxaban compared with enoxaparin in preventing VTE in patients undergoing hip fracture surgery.

Materials and methods: This single-center, retrospective cohort study included patients who received either oral rivaroxaban or subcutaneous injections of enoxaparin for VTE prophylaxis following hip fracture surgery from 2020 to 2023. The data obtained included patient demographics, fracture classification, time to surgery, and procedures performed. The main outcomes assessed were the incidence of VTE and hemorrhagic events and death within 30 days of surgery. The daily costs of the two types of medications were also recorded.

Results: A total of 166 patients were included. The incidence of VTE was 9.5% in the rivaroxaban group and 26.61% in the enoxaparin group. Hemorrhagic events occurred in 9.52% and 1.61% of patients in the rivaroxaban and enoxaparin groups, respectively. No deaths occurred in either group. The average daily cost of rivaroxaban was 26.49 ± 4.77 Chinese yuan, while that of enoxaparin was 75.24 ± 18.54 Chinese yuan.

Conclusion: In this cohort study, rivaroxaban was found to be significantly more effective than enoxaparin in reducing postoperative VTE after hip fracture, but it was associated with a higher risk of hemorrhagic events. Additionally, the average daily cost of rivaroxaban was lower. To identify patients who will derive the maximum advantages from this treatment, larger prospective studies are needed.

KEYWORDS

hip fractures, venous thromboembolism, rivaroxaban, enoxaparin, cost

Introduction

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a significant cause of morbidity and mortality subsequent to hip fractures (1). In the absence of preventive measures, the incidence of VTE after hip fracture is estimated to reach 16.6% (2). The perioperative incidence of VTE in patients with hip fracture can be reduced by implementing effective anticoagulation strategies, typically involving the utilization of anticoagulants such as low-molecular-weight heparin (LMWH) (3), aspirin (4), or warfarin (3).

In recent years, the utilization of direct oral anticoagulants (DOACs) in orthopedic surgery has significantly expanded (3, 5, 6). DOACs offer advantages due to their oral administration, predictable pharmacological profile, and lack of required monitoring. Moreover, multiple studies have demonstrated that compared with conventional anticoagulants, DOACs are associated with lower rates of VTE without an increased risk of hemorrhage (7, 8). However, the evidence supporting the use of rivaroxaban for VTE prophylaxis following hip fracture surgery is limited, with LMWH being the preferred form of anticoagulation (9, 10). This study aimed to compare rivaroxaban with enoxaparin for preventing VTE in terms of effectiveness, safety, and cost in patients undergoing hip fracture surgery.

Methods and materials

Population

This single-center, retrospective, cohort study included patients who received either rivaroxaban or enoxaparin for VTE prophylaxis following hip fracture surgery from 1 January 2020 to 31 December 2022.

The inclusion criteria were as follows: participants were ≥ 18 years of age, had a confirmed diagnosis of either femoral neck or intertrochanteric femoral fractures, and received rivaroxaban anticoagulant therapy or enoxaparin anticoagulant therapy during the perioperative period.

Patients with any of the following characteristics were excluded: missing data, previous PE or DVT, previous major hemorrhage, underlying malignancy, or inherited coagulation disorder. All patients were followed up for 30 days postoperatively.

Clinical parameters

The following data were obtained: patient demographics, fracture classification, American Society of Anesthesiologists (ASA) classification, time to surgery, surgical procedures, and hospital stay. The outcomes assessed were the incidence of PE or DVT and hemorrhagic events and death within 30 days of surgery. PE was diagnosed using computed tomography pulmonary angiography, and DVT was diagnosed using duplex ultrasound scanning. Each patient received a postoperative lower limb venous ultrasound examination. Computed tomography pulmonary angiography was performed for patients with symptomatic PE. Hemorrhagic events include major bleeding, clinically relevant non-major bleeding (CRNMB), and minor bleeding. Major bleeding was defined as a decrease in the hemoglobin level of ≥ 2 g dl⁻¹, bleeding leading to transfusion, bleeding at a critical site, or bleeding contributing to death (11). CRNMB was defined as bleeding not meeting the criteria for major bleeding but associated with medical intervention, temporary cessation of study treatment, patient discomfort such as pain, or impairment of activities of daily living (12). Minor

bleeding was defined as bleeding not meeting the criteria for either major bleeding or CRNMB.

In the event of death, the coroner's report, hospital, and general practice records were reviewed to establish the cause of death. During the study, the cost of rivaroxaban or enoxaparin was also recorded.

Administration regime

Rivaroxaban (Xarelto, Bayer) was administered at 10 mg qd beginning 6–10 h after surgery. Enoxaparin (Clexane, Sanofi) was administered via subcutaneous injection at a dosage of 4,000 IU qd beginning 6 h after surgery. The treatment duration for both groups was set to a standardized period of 30 days.

Statistical analysis

Multivariate analysis was performed using GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, CA, USA). The relevant data are expressed as percentages, means, and standard deviations. Parametric data were analyzed via Student's *t*-test, whereas categorical data were assessed using the chi-square test. The presentation of relative risk (RR) includes a 95% confidence interval (CI) and *P*-value. Power analysis was also performed (13).

Ethical approval

This study was conducted retrospectively, utilizing anonymous data that had been previously collected during patient assessments or for service evaluation. The local ethics committee reviewed the study proposal and determined that ethical approval was not required.

Results

This retrospective cohort study included 166 patients, with 42 patients receiving rivaroxaban treatment and 124 patients receiving enoxaparin treatment. All participants were closely monitored for 30 days as part of our final analysis.

The mean age of the patients in the rivaroxaban group was 77.95 ± 12.91 years, and the mean age of those in the enoxaparin group was 76.27 ± 11.00 years; no significant difference was found between the two groups. The male–female ratio was 18:24 in the rivaroxaban group and 56:68 in the enoxaparin group. There were no significant differences in sex composition between the two groups.

The enoxaparin group included 41 patients with femoral neck fractures, 81 patients with intertrochanteric fractures, and 2 patients with subtrochanteric fractures. Proximal femoral nail antirotation (PFNA) was performed in 82 patients, accounting for 66.13% of all patients. This was followed by total hip

arthroplasty (THA) in 41 patients and the use of the femoral neck system (FNS) in 1 patient. The mean time to surgery was 2.24 ± 0.93 days. The rivaroxaban group included 18 patients with femoral neck fractures and 24 patients with intertrochanteric fractures. PFNA was performed in 24 patients. This was followed by THA in 18 patients. The mean time to surgery was 2.37 ± 1.53 days. The baseline demographic and clinical characteristics are presented in Table 1.

The rivaroxaban group had a VTE incidence of 9.52% (95% CI: 0.04–0.22), that of the enoxaparin group was 26.61% (95% CI: 0.19–0.35), and the RR was 0.36 (95% CI: 0.14–0.87). The incidence of VTE in the rivaroxaban group was significantly lower than that in the enoxaparin group ($P < 0.05$), and the statistical power was approximately 81%. PE was not observed in either group ($P > 0.05$).

Hemorrhage occurred in 9.53% (95% CI: 0.04–0.22) of patients in the rivaroxaban group and 1.61% (95% CI: 0.01–0.06) of patients in the enoxaparin group (RR: 5.90, 95% CI: 1.29–26.76, $P = 0.017$). No major bleeding was observed in either group. The statistical power was approximately 53.9%.

The average daily cost of rivaroxaban was 26.49 ± 4.77 Chinese yuan, whereas that of enoxaparin was 75.24 ± 18.54 Chinese yuan. The average daily cost of rivaroxaban was lower than that of enoxaparin ($P < 0.05$), and the statistical power was approximately 100%. The efficacy and safety outcomes are shown in Table 2.

TABLE 1 Baseline demographic and clinical characteristics.

Characteristic	Rivaroxaban, <i>n</i> = 42	Enoxaparin, <i>n</i> = 124	<i>P</i> -value
Age, years	77.95 ± 12.91	76.27 ± 11.00	0.42
Gender			0.86
Male	24	68	
Female	18	56	
ASA Scores			0.79
ASA I	0	0	
ASA II	18	57	
ASA III	24	69	
ASA IV	0	0	
Fracture classification			0.10
Garden III	15	38	
Garden IV	1	3	
Russell–Taylor IA	1	1	
Russell–Taylor IIA	0	1	
Evans–Jensen II	1	4	
Evans–Jensen III	7	39	
Evans–Jensen IV	2	20	
Evans–Jensen V	11	16	
Evans–Jensen R	1	0	
Surgery procedure			0.001
Total hip arthroplasty	23	41	
FNS	3	1	
PFNA	16	82	
Time to surgery, days	2.24 ± 0.93	2.37 ± 1.53	0.59

ASA, American Society of Anesthesiologists.

TABLE 2 Efficacy and safety outcomes in all patients.

Outcomes	Rivaroxaban, <i>n</i> = 42	Enoxaparin, <i>n</i> = 124	<i>P</i> -value
All venous thromboembolism	4 (9.52%, 95% CI: 0.04–0.22)	33 (26.61%, 95% CI: 0.19–0.35)	0.02
Pulmonary embolism	0	0	
Deep venous thrombosis	4 (9.52%, 95% CI: 0.04–0.22)	33 (26.61%, 95% CI: 0.19–0.35)	0.02
Hemorrhagic events	4 (9.52%, 95% CI: 0.04–0.22)	2 (1.61%, 95% CI: 0.004–0.06)	0.017
Major bleeding	0	0	
CRNBM ^a	2 (4.76%, 95% CI: 0.01–0.16)	1 (0.8%, 95% CI: 0.001–0.04)	0.17
Minor bleeding	2 (4.76%, 95% CI: 0.01–0.16)	1 (0.8%, 95% CI: 0.001–0.04)	0.17
Cost daily (Chinese yuan)	26.49 ± 4.77	75.24 ± 18.54	<0.0001
All-cause mortality	0 (0%)	0 (%)	>0.99

^aCRNMB, clinically relevant non-major bleeding.

Discussion

In this study, the administration of rivaroxaban for preventing VTE after hip fracture surgery demonstrated a lower incidence of VTE than did the administration of enoxaparin. The use of rivaroxaban for the prevention of postoperative VTE in patients with lower limb fractures is controversial. Some studies suggest that DOACs exhibit comparable efficacy to LMWH in the prevention of VTE following lower limb orthopedic surgery (14–18). In these studies, the results of direct comparisons between rivaroxaban and enoxaparin indicate that both have similar efficacy in preventing venous thromboembolism (16, 17). However, the results of this study are quite different because rivaroxaban produced a reduced incidence of VTE. These findings are similar to those of previous evaluations of the effectiveness of rivaroxaban in preventing VTE in patients undergoing lower limb orthopedic surgery, where the incidence of VTE was lower in patients treated with rivaroxaban than in those treated with enoxaparin (19–21). Although the effectiveness of rivaroxaban and enoxaparin is debated, existing studies have consistently shown that rivaroxaban is not inferior to enoxaparin in preventing VTE.

The incidence rates of VTE in the rivaroxaban and enoxaparin groups were 9.52% (95% CI: 0.04–0.22) and 26.61% (95% CI: 0.19–0.35), respectively, which were higher than those reported in other studies (22). In a study conducted by Tang et al. (10), the incidence of VTE was found to be significantly lower with the administration of rivaroxaban (5.2%) than with the administration of enoxaparin (14.7%). Differences in study design may account for the variation in rates of VTE reported in both the rivaroxaban and enoxaparin groups in the present study. Patients participating in randomized controlled trials (RCTs) are subjected to regular examinations for VTE, which can result in the identification of patients with asymptomatic PE and DVT. Although our study was not an RCT but rather a retrospective cohort study, our department ensured the safety of patients by conducting postoperative VTE examinations for all patients undergoing lower limb orthopedic surgery. This ultimately led to a higher incidence of VTE, as more patients with asymptomatic VTE were discovered.

Another reason might be related to compliance. One study (23) investigated the association between patient compliance and the efficacy of LMWH in patients undergoing hip fracture surgery and receiving anticoagulation treatment. This study of 1,214 patients with hip fractures categorized participants into three compliance groups: low (<14 days, 64.7%), normal (14–27 days, 19.0%), and high (≥ 28 days, 16.3%). Postoperative VTE incidence significantly differed across groups, at 9.6%, 5.4%, and 4.2%, respectively ($P = 0.013$). Multivariate analysis revealed that low compliance (<14 days) was an independent risk factor for VTE (OR = 2.77, 95% CI: 1.27–6.04). This study further emphasized that compliance plays a critical role in influencing VTE incidence and that low compliance with treatment can increase the incidence of VTE. Bergqvist et al. (24) studied compliance with VTE prevention therapy in patients with hip fractures undergoing total hip arthroplasty and knee arthroplasty. The results showed that treatment via injection negatively affected patient compliance. Furthermore, insufficient basic healthcare institutions and limited family care have also contributed to the low compliance of patients in China (25).

Another reason for the higher incidence of VTE in the enoxaparin group might be related to the dose. To treat thromboprophylaxis, the administration of enoxaparin at a fixed daily dose of 4,000 IU is recommended (26). While standard doses can be used in most patients, patients at the extremes of weight are at risk for either overdosing (low-body-weight patients) or underdosing (high-body-weight patients) (27, 28).

The mortality rate for both groups of patients in this study was zero. This was mainly due to the improved detection and subsequent treatment of VTE in postsurgical patients, which helped prevent the occurrence of PE. Both DVT and PE are associated with potentially significant morbidity and mortality (29).

The incidence rates of hemorrhage in the rivaroxaban and enoxaparin groups were 9.53% and 1.61%, respectively. Four patients in the rivaroxaban group and two patients in the enoxaparin group experienced hemorrhagic events. No patients in either group experienced any major bleeding. The incidence of minor bleeding in the rivaroxaban group was significantly greater than that in the enoxaparin group. However, the statistical power was only 59.6%, indicating that the sample size was insufficient to reliably detect the observed difference. This trend toward a potential risk of hemorrhage has not been reported in earlier studies of elective orthopedic surgery (10, 22).

Most patients with hip fractures are elderly and physically weak and have multiple comorbidities, making them prone to fatal hemorrhage. Although no major bleeding was observed in this study, further research is warranted to investigate this situation.

While LMWH must be administered via subcutaneous injection due to its pharmaceutical properties, this administration method may lead to low patient compliance post-discharge and to challenges in completing the entire anticoagulation treatment course (30).

In contrast, oral administration is the method of administration for rivaroxaban. The enhanced convenience and the fact that elderly patients do not require coagulation function monitoring and dose adjustment may help improve compliance with long-term anticoagulant therapy after discharge.

Hence, there is a greater probability that individuals will adhere to their healthcare provider's guidance and maintain the use of rivaroxaban for VTE prevention, potentially resulting in earlier discharge. In addition, rivaroxaban is less expensive than enoxaparin. The average daily cost of rivaroxaban in the present study was lower than that of enoxaparin (26.49 ± 4.77 vs 75.24 ± 18.54 Chinese yuan, respectively).

Rivaroxaban not only is a more affordable medication but also requires less care time and hospital resources for management. In Australia, the cost of a course of rivaroxaban post-THA is \$99.6, whereas that of enoxaparin is \$151.1 (31). According to calculations using data from the American healthcare system, using rivaroxaban instead of enoxaparin can reduce treatment costs by \$262 per patient (32).

The effectiveness of rivaroxaban makes it a cost-effective drug for the prevention of VTE, despite the potential risk of minor bleeding.

Our research has several limitations. First, due to the retrospective study design, there were limitations in terms of patient randomization and control. Senior clinical doctors decide whether to prescribe rivaroxaban based on the presence of risk factors for thromboembolism and consider the bleeding risk. Therefore, the rivaroxaban group in this study is likely to represent a selected group of patients who are likely to benefit from this treatment. Our study was limited by a sample size of 166 patients, and the sample size was not estimated in advance. A larger sample size is needed to detect clinically significant differences between the two groups. Because enoxaparin is still one of the first-line treatments for VTE prevention in China, only a small number of patients receive rivaroxaban.

Conclusion

In this retrospective cohort study, rivaroxaban was found to be more effective than enoxaparin in reducing the risk of VTE after hip fracture surgery. However, a trend toward an increased risk of hemorrhage was noted, which necessitates further investigation. However, we discovered that the cost-effectiveness of rivaroxaban, considering its effectiveness in reducing VTE, surpassed that of enoxaparin. Therefore, after the patients most likely to benefit from this treatment are identified and the potential risk of bleeding is reduced, rivaroxaban may be an economically effective and safe alternative for routine thromboprophylaxis following hip fracture surgery. Future studies involving a larger number of patients are necessary to determine which patients are most likely to benefit from this treatment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XZ: Conceptualization, Investigation, Project administration, Writing – review & editing, Writing – original draft. LW: Data curation, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. YC: Data curation, Resources, Writing – review & editing. LL: Software, Writing – review & editing. ZZ: Investigation, Methodology, Writing – review & editing. CX: Conceptualization, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

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