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Research Article
Comparing the Efficacy, Safety and Cost of the Anticoagulants: Rivaroxaban and Nadroparin in Hip Replacement Surgery

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Abstract

Background and Objective: Many anticoagulants have significant drawbacks: Aspirin has limited efficacy, warfarin is highly effective but the dosage must be monitored and adjusted carefully and dabigatran is effective but may be lethal. The current study compares the efficacy of rivaroxaban, low-dose nadroparin calcium and high-dose nadroparin calcium for thromboprophylaxis in patients after total hip replacement (THR) surgery. **Materials and Methods:** A total of 831 THR surgery patients were enrolled in this randomized, three-arm study (n = 277 for each of three groups). Group I patients received rivaroxaban (10 mg), group II patients received low-dose nadroparin calcium (3,000 anti-Xa IU kg^{-1} b.wt.) and group III patients received high-dose nadroparin calcium (6,500 anti-Xa IU kg^{-1} b.wt.). Follow-up visits with patients were conducted 40 days after the intervention. Outcomes were measured using D-dimer test assays, angiography and digital color Doppler scanner ultrasound. Additionally, the cost of treatment was calculated for each patient. A two-tailed paired t-test and Dunnett's multiple comparison tests were used to compare measured outcomes and the cost of therapy between groups I and II and between groups I and III at a 95% confidence level. **Results:** Efficacy outcomes for group I were superior to those of group II ($p \leq 0.05$ for all outcomes) and comparable to those of group III ($p > 0.05$ for all outcomes). The 10 mg rivaroxaban treatment had a major bleeding event in the gastrointestinal tract and liver. Adverse effects of nadroparin included hyperkalemia, skin rash and leg weakness. The cost of therapy was highest for group III and lowest for group I. **Conclusion:** Rivaroxaban and nadroparin are both effective as thromboprophylactic drugs in patients following THR surgery and have few adverse effects. Physicians may successfully use any of these therapies according to the patient's condition.

Key words: Hyperkalemia, nadroparin, phlebotomize commencement, rivaroxaban, thromboprophylaxis

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) are the current guidelines for anticoagulant therapy following hip-replacement surgery. The guidelines are recommending treatment with low molecular weight heparin (LMWH) fondaparinux (Grade: 1A) or a vitamin K antagonist (VKA, Grade: 1B) to prevent venous thromboembolism following total hip replacement (THR) surgery. The guidelines also recommend the use of an anticoagulant agent or agents for a minimum of 10 days[1]. With this course of treatment, there is a 20-40% risk of patients developing deep vein thromboembolism (DVTS)[2]. Continuing treatment with a Grade 1A agent for 35 days after surgery[1] can reduce the risk of DVTS. However, most patients do not continue anticoagulant prophylaxis treatment after discharge from the hospital[3] and because hospital stay durations are decreasing (maximum 5-6 days), few patients receive the required minimum 10 days of anticoagulant agent(s) treatment recommended by the guidelines[1]. The frequency of treatment with once-daily (OD) oral aspirin after hospital discharge has significantly increased, despite limited efficacy, because of the convenience of administration[3]. Warfarin[4], phenprocoumon[2], and acenocoumarol[5] have high efficacy but careful dose adjustments are required. Dabigatran is an effective anticoagulant, however, a very high (potentially lethal) dose is required for optimal efficacy[2]. A new oral anticoagulant treatment is needed to prevent venous thromboembolism following THR surgery. German guidelines recommend LMWH as the standard thromboprophylaxis agent[5,6]. Nadroparin calcium is LMWH calcium and the leading choice for DVTS prophylaxis and treatment[7]. Rivaroxaban is a direct factor Xa inhibitor that provides consistent and predictable anticoagulation[4]. Weitz *et al.*[8], study have reported that rivaroxaban is effective in preventing DVTS in patients following orthopedic surgeries.

The objective of the current study was to compare the efficacy of rivaroxaban with low and high doses of nadroparin calcium for thromboprophylaxis in patients following THR surgery. A secondary objective was to evaluate the safety of rivaroxaban and nadroparin calcium during treatment and follow-up visits by comparing them.

MATERIALS AND METHODS

The study was carried out from January, 2013-March, 2016 at Shanghai Jiangong Hospital, Shanghai, China.

Materials: Rivaroxaban (Xarelto® 10 mg) tablets were purchased from Janssen Pharmaceuticals, Inc. (Raritan, NJ, USA). Nadroparin calcium (Fraxiparine™/Fraxiparine Forte™) prefilled syringes were purchased from GlaxoSmithKline (Shanghai, China). Aspirin was purchased from Dexcel Pharma Ltd., UK.

Ethical statement: The ethics committee for human experiments of Shanghai Jiangong Hospital, Shanghai, China approved the experimental protocol, ethical guidelines for biomedical research on human participants were followed in accordance with Chinese law[9].

Exclusion criteria: Individuals who did not sign the informed consent form, refused follow-up visits or refused to participate were excluded from the study. Patients who had allergic reactions to nadroparin, a medical history of heparin-induced thrombocytopenia, a major blood clotting disorder, active bleeding were excluded from the study. Individuals with other conditions who were at severe risk of bleeding, acute infective endocarditis, bacterial infection of the heart, bleeding due to active stomach or duodenal ulcers, eye diseases or disorders due to diabetes or bleeding, head injuries, brain operations, spinal cord operations, eye operations, ear operations, chronic renal failure, hypertension or who received general anesthesia were excluded from the study.

Inclusion criteria: A total of 989 patients with DVTS, pulmonary embolism (PE), proximal deep vein thrombosis (PDVT), distal deep vein thrombosis (DDVT) or calf muscle vein thrombosis (CMVT) following THR surgery were included in the study. Patients were randomly divided into three groups as described in Table 1. All patients signed a written informed consent form approved by the ethical committee of Shanghai Jiangong Hospital, Shanghai, China.

Prior sample size calculations: Using Eq. 1, the sample population was calculated as 277 for each of the three groups[10]:

$$n = \frac{DEFF \times Np\,(1-p)}{d^2 / Z^2_{1-\alpha/2} \times (N-1) + p(1-p)} \quad (1)$$

Where:

n = Sample size

N = Total number of patients assessed for eligibility (989)

Table 1: Demographic characteristics, pathology, and treatments of enrolled patients

	Group I	Group II	Group III
Treatments	Rivaroxaban 10 mg OD	Nadroparin calcium low dose	Nadroparin calcium high dose
Sample size	277 (100)	277 (100)	277 (100)
Gender			
Male	122 (44)	142 (51)	139 (50)
Female	155 (56)	135 (49)	138 (50)
Age (mean±SD)	60.87±3.51	60.96±3.48	61.19±3.51
BMI (kg m^{-2}) (mean±SD)	27.12±1.2	26.23±1.3	29.15±1.5
VT	65 (23)	55 (20)	59 (21)
PE	67 (24)	68 (24)	71(26)
PDTE	45 (16)	49 (18)	41(15)
DDVT	54 (20)	69 (25)	52 (18)
CMVT	35 (13)	30 (11)	33 (12)
Death	0 (0)	0 (0)	0 (0)
Patients on oral aspirin	5 (2)	7 (3)	9 (3)
KT	11 (4)	6 (2)	21 (8)
Serum potassium level (mEq L^{-1}) (Mean±SD)	3.36±0.24	3.80±0.25	3.39±0.25

Data are given as numbers (percentage), CMVT: Calf muscle vein thrombosis, DDVT: Distal deep vein thrombosis, KT: Known thrombophilia, OD: Once a day, PDVT: Proximal deep vein thrombosis, PE: Pulmonary embolism, VT: Venous thromboembolism, All patients were of China PR origin, *Body mass index: $\text{BMI} = \frac{\text{Weight}}{\text{Height}^2}$

P = Hypothesized percentage frequency of efficacy outcome in patients (50±5%)
d = ±5%
DEFF = Design effect for cluster survey (1)
Confidence level = 95%
$Z_{1-\alpha/2}$ = The standard normal variant (1.96)

Patients were randomized into three groups of 277 patients each. A flow diagram showing the three arms of the study is presented in Fig. 1.

Interventions: Treatment was initiated 8 h after THR surgery. Group I patients received a 10 mg tablet of rivaroxaban OD, group II patients received the low dose of nadroparin calcium (3,000 anti-Xa IU kg^{-1} b.wt.,) as a subcutaneous (S/c) injection OD and group III patients received the high dose of nadroparin calcium (6,500 anti-Xa IU kg^{-1} b.wt., S/c injection, OD). The treatment period was 35 days[1]. Concomitant administration of 75 mg aspirin was permitted during treatment.

Efficacy outcome measures: DVTS, non-fatal PE, death from any cause up to 36 days (range: 29-42 days), major venous thromboembolism, composite of proximal DVTS, incidence of DVTS and incidence of symptomatic venous thromboembolism up to 36 days (range: 29-42 days) were measured by members of the regulation of coagulation committee of the PR China. All diagnostic procedures were carried out by D-dimer test assay or chemiluminescence assay (Nanjing Norman Biological Technology Co., Ltd., Nanjing, China) and portable full digital color Doppler scanner ultrasound (HUC-300; Healicom Medical Equipment Co., Ltd, Shanghai, China)[11]. In cases of nonfatal PE, angiography (Nanjing Jusha Display Technology Co., Ltd., Nanjing, China) was employed[12].

Safety assessment: Follow-up visits were conducted 40 days after the conclusion of treatment.

Major bleeding event: An important measure of safety is the prevalence of a major bleeding event in the gastrointestinal tract, liver and spinal cord, following the primary intervention and up to 2 days after the final intervention. A portable full digital color Doppler scanner ultrasound was used to record observations. A postoperative decrease in hemoglobin (Hb) was used to estimate the a major bleeding event, defined as requiring a transfusion of at least two units of whole blood[13].

Secondary safety outcomes: During the intervention and follow-up visits, secondary safety outcomes (i.e., death, ischemic stroke, myocardial infarction and hyperkalemia) were noted[12]. Hyperkalemia was defined as a serum potassium level >6.0 mEq L^{-1}. A serum potassium level between 5.1-6.0 mEq L^{-1} was defined as mild hyperkalemia[14].

Other safety outcomes: Other safety outcomes , such as injection site hematoma, fever, itching, skin rash, anaphylactic shock, cutaneous necrosis, epistaxis, hematuria, bowel dysfunction, urinary bladder dysfunction, leg weakness, numbness, melena, purpura and thrombocytopenia were recorded at follow-up visits[15].

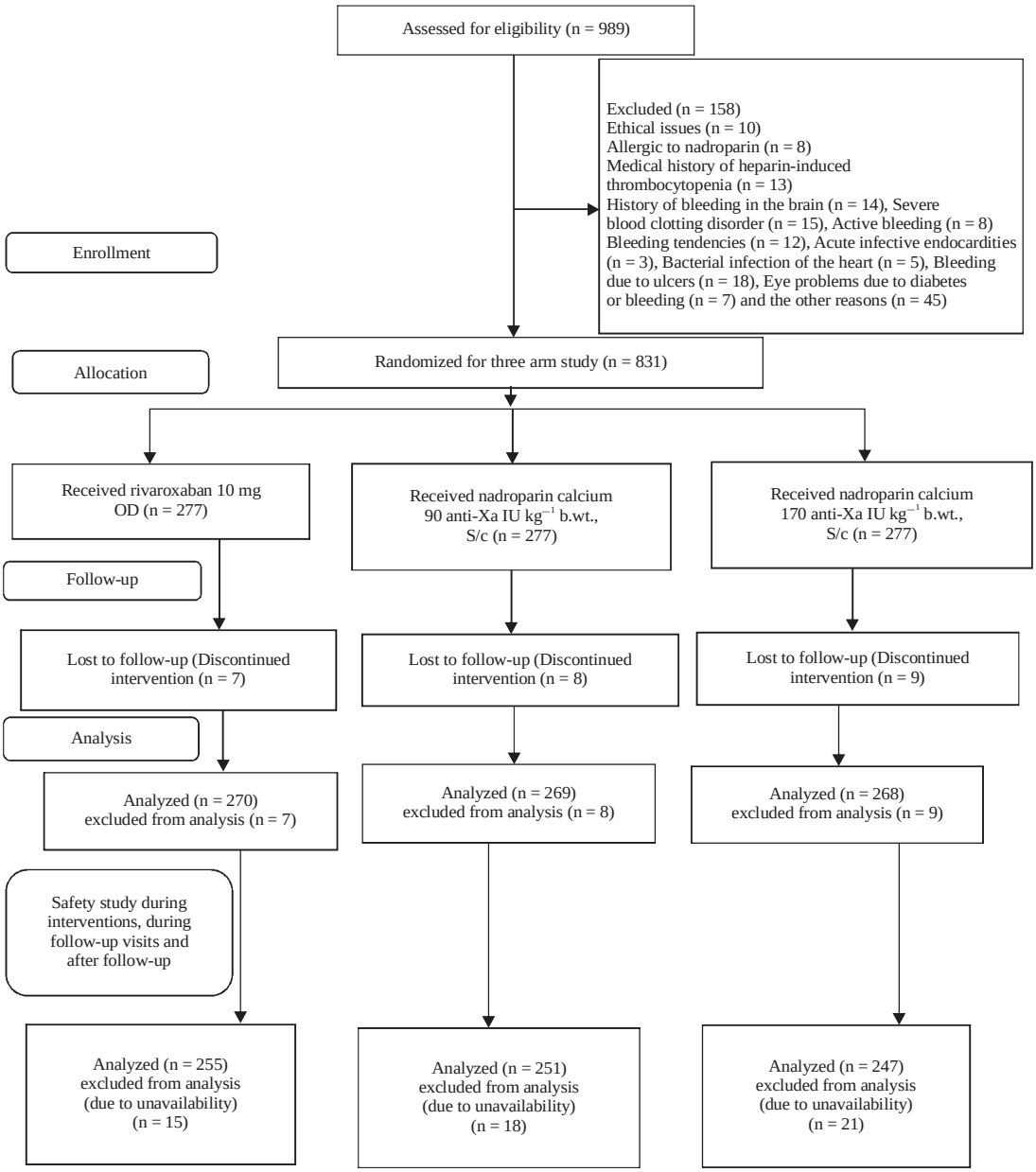

Fig. 1: Flow diagram of the three-arm study, OD: Once per day, S/c: Subcutaneous

Treatment cost: The total cost of treatment as well as the individual costs attributable to medications, interventions, pathology, loss of wages and hospital stays were calculated for each patient[16].

Statistical analysis: Using InStat Statistica software (GraphPad Software, Inc., La Jolla, CA, USA). A two-tailed paired t-test, in which $\beta = 1$ and $\alpha = 0.05$[17], followed by Dunnett's multiple comparison test, in which $q>2.361$, were used to compare efficacy outcome measures, a major bleeding event, secondary safety outcomes, other safety outcomes and the cost of therapy between groups I and II and between groups I and III[18]. A 95% confidence level was considered significant. For the purpose of the statistical analysis, the occurrence of an event was coded as 1 and the absence of an event was coded as 0.

RESULTS

In total, 7 patients from group I, 8 patients from group II and 9 patients from group III discontinued treatment during the course of the study. The remaining 270, 269 and

Table 2: Efficacy outcomes during the 40 days follow-up

	Groups						
Outcome measures	I	II	p-value*	q-value*	III	p-value¶	q-value¶
Sample size	270 (100)	269 (100)			268 (100)		
DVTS	5 (2)	12 (5)	0.0079	3.145	6 (2)	0.3182	N/A
Proximal DVTS	0 (0)	1 (0.4)	0.318	N/A	1 (0.4)	0.31	N/A
Distal DVTS	5 (2)	11 (4)	0.014	2.613	5 (2)	N/A	N/A
Nonfatal PE	2 (1)	4 (2)	0.1577	N/A	5 (2)	0.0833	N/A
Death from any cause up to 36 days[a]	7 (3)	15 (6)	0.0045	2.851	6 (2)	0.3182	N/A
Major venous thromboembolism	3 (1)	15 (6)	0.0005	4.581	4 (2)	N/A	N/A
Composite of proximal DVTS	2 (1)	11 (4)	0.0026	3.512	3 (1)	0.31	N/A
Incidence of DVTS	1 (0.4)	12 (5)	0.0008	3.912	3 (1)	0.310	N/A
Incidence of symptomatic venous thromboembolism up to 36 days[a]	2 (1)	17 (6)	0.0001	5.291	5 (2)	0.31	N/A

DVTS: Deep vein thromboembolism, N/A: Not applicable, PE: Pulmonary embolism, Data are given as numbers (%), [a]Range: 29-42 days, *Between groups I and II, ¶Between groups I and III

Table 3: Effects of rivaroxaban and nadroparin for internal bleeding

Prevalence of a major bleeding event events		Groups I	II	p-value*	q-value*	III	p-value¶	q-value¶
Sample size		255 (100)	251 (100)			247 (100)		
Gastrointestinal tract	X	45 (20)	2 (1)	<0.0001	8.763	4 (2)	<0.0001	7.983
	Y	35 (16)	2 (1)	<0.0001	6.593	1 (0.4)	<0.0001	7.763
Liver	X	15 (7)	3 (1.5)	0.0005	5.156	4 (1)	0.0008	5.059
	Y	7 (3)	2 (1)	0.0251	3.519	3 (1)	0.0453	2.918
Spinal cord	X	12 (5)	1 (0.5)	0.0008	5.06	3 (1)	0.0025	2.756
	Y	9 (4)	1 (0.5)	0.0045	5.216	2 (1)	0.0079	2.591
Hemoglobin (g dL^{-1}) (mean±SD)	Preoperative	12.1±1.45	12.15±1.49	N/A	N/A	12.19±1.51	N/A	N/A
	Post-operative	10.1±0.95	10.2±1.05	N/A	N/A	10.25±1.12	N/A	N/A
	Transfusions required	75 (29)	45 (18)	<0.0001	8.765	15 (6)	<0.0001	12.221

N/A: Not applicable, Data are represented as numbers (%) , *Between groups I and II, ¶Between groups I and III, X: Following the primary intervention, Y: Up to 2 days after the concluding intervention

268 patients of groups I, II and III, respectively, were included in the analysis (Table 2).

In total, 15 subjects from group I, 18 from group II and 21 from group III were unavailable for follow-up visits 40 days after the conclusion of treatment and were thus not included in the analysis. The remaining patients were included in the safety assessment.

Group I had significantly higher ($p \leq 0.05$) a major bleeding event in the gastrointestinal tract compared to the other groups (Table 3). Group III displayed a significantly higher ($p \leq 0.05$) incidence of hyperkalemia compared to the other groups (Table 4). Other adverse effects did not differ among groups (Table 5). Group III had the greatest number of hospitalized patients during follow-up visits, while group II had the least (Fig. 2).

Compared to group I, the costs attributable to medications, interventions, pathology, loss of wages and hospital stays as well as the total costs were significantly higher ($p \leq 0.05$) in groups II and III (Table 6).

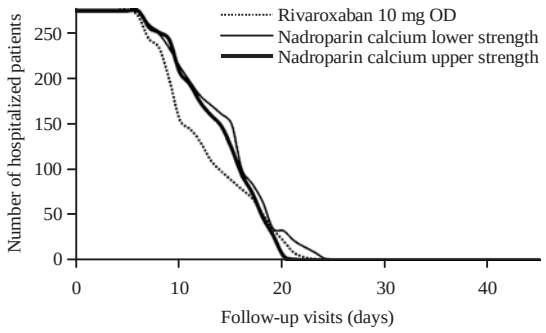

Fig. 2: Number of hospitalized patients during follow-up visits

DISCUSSION

No significant differences in efficacy were observed between the 10 mg rivaroxaban tablet and high-dose (6,500 anti-Xa IU kg^{-1} b.wt.,) nadroparin calcium S/c treatments. Previous studies have found that rivaroxaban treatment than a high dose (5,700-7,600 IU kg^{-1} b.wt.,) of

Table 4: Secondary safety outcomes: Analysis at 40 days follow-up

		Groups						
Outcome measures		I	II	p-value*	q-value*	III	p-value¶	q-value¶
Sample size		255 (100)	251 (100)			247(100)		
Death	X	2 (1)	0 (0)	0.1577	N/A	0 (0)	0.1577	N/A
	Y	3 (1)	1 (0.4)	0.1577	N/A	0 (0)	0.083	N/A
Ischemic stroke	X	1 (0.4)	1 (0.4)	N/A	N/A	0 (0)	0.3183	N/A
	Y	1 (0.4)	0 (0)	0.1577	N/A	0 (0)	0.1577	N/A
Myocardial infarction	X	2 (1)	1 (0.4)	0.3183	N/A	0 (0)	0.1577	N/A
	Y	1 (0.4)	0 (0)	0.1577	N/A	0 (0)	0.1577	N/A
Hyperkalemia	X	1 (0.4)	8 (3)	0.0079	5.163	35 (14)	0.0001	9.616
	Y	0 (0)	1 (0.4)	0.3183	N/A	3 (1)	0.083	N/A
Mild hyperkalemia	X	2 (1)	12 (5)	0.0014	3.59	75 (30)	0.0001	10.521
	Y	0(0)	2(1)	0.1577	N/A	13 (1)	0.0003	5.269

N/A: Not applicable, Data are given as numbers (%), *Between groups I and II, ¶Between groups I and III, X: During intervention, Y: During follow-up visits

Table 5: Analysis of adverse effects during 40-day follow-up

	Groups						
Outcome measures	I	II	p-value*	q-value*	III	p-value¶	q-value¶
Sample size	255 (100) N (%)	251 (100) N (%)			247 (100) N (%)		
Injection site hematoma	N/A	5 (2)	N/A	N/A	14 (6)	N/A	N/A
Fever	3 (1)	9 (4)	0.014	2.695	21 (9)	0.0001	5.612
Itching	3 (1)	11 (4)	0.0045	3.982	35 (14)	0.0001	7.223
Skin rash	5 (2)	15 (6)	0.015	2.701	27 (11)	0.0001	6.513
Anaphylactic shock	0 (0)	0 (0)	N/A	N/A	1 (0.4)	0.3183	N/A
Cutaneous necrosis	1 (0.4)	5 (2)	0.0453	2.613	17 (7)	0.0001	4.721
Epistaxis	1 (0.4)	1 (0.4)	N/A	N/A	5 (2)	0.0453	3.973
Hematuria	2 (1)	5 (2)	0.0833	N/A	19 (8)	0.0001	4.832
Bowel dysfunction	0 (0)	3 (1)	0.083	N/A	5 (2)	0.0250	2.916
Urinary bladder dysfunction	2 (1)	7 (3)	0.0251	2.921	12 (5)	0.0014	3.156
Leg weakness	2 (0.8)	15 (6)	0.003	4.981	35 (14)	0.0001	6.723
Numbness	3 (0.8)	5 (2)	0.1577	N/A	12 (5)	0.0025	3.018
Melena	0 (0)	4 (2)	0.0453	2.615	5 (2)	0.0250	2.551
Purpura	1 (0.4)	1 (0.4)	N/A	N/A	15 (6)	0.0002	8.514
Thrombocytopenia	1 (0.4)	2 (0.8)	0.3183	N/A	2 (1)	0.3183	N/A

N/A: Not applicable, Data are given as numbers (%), *Between groups I and II, ¶Between groups I and III

Table 6: Cost analysis of rivaroxaban and low dose and high dose nadroparin treatments

	Cost (Euros) (mean±SD)						
Groups	I	II	p-value*	q-value*	III	p-value¶	q-value¶
Sample size (n)	255 (100)	251 (100)			247 (100)		
Drug	16.31±1.15	42.97±2.72	<0.0001	5.701	74.01±4.77	<0.0001	7.802
Intervention	0.20±0.07	398.51±5.82	<0.0001	15.602	402.38±5.12	<0.0001	22.690
Pathology	127.47±3.80	129.23±6.49	0.0004	3.012	130.07±7.25	0.0005	3.121
Loss of wages	4.18±1.83	7.15±1.66	<0.0001	5.512	7.89±1.40	<0.0001	5.623
Hospital stay	4.65±0.52	7.60±3.120	<0.0001	5.021	12.98±1.19	<0.0001	6.013
The total	152.86±6.01	585.67±8.36	<0.0001	6.121	628.26±11.03	<0.0001	7.114

*Between groups I and II, ¶Between groups I and III

nadroparin calcium[19]. Efficacy outcome measures were better with the 10 mg rivaroxaban OD treatment than the low-dose (3,000 anti-Xa IU kg^{-1} b.wt.,) nadroparin calcium S/c injections.

The current study used a randomized, three-group design and each group consisted of 277 patients. Dunnett's multiple comparison test was used as a *post hoc* test. Previous studies included fewer participants[19,20] and used ANCOVA[16], the chi-square test[19], Fisher's exact test or Student's t-test[20] in their statistical analyses. A small sample size increases the chances of α-error[21]. In comparison to other *post hoc* tests, Dunnett's multiple comparison test is more accurate for predicting group differences in outcomes. The size of the sample population was sufficient to measure the outcomes of interest.

Patients in the rivaroxaban treatment group required significantly more blood transfusions than the low- and high-dose nadroparin calcium groups. A major bleeding event were observed in the rivaroxaban treatment group[22] and serious bleeding event were difficult to manage. To date, there is no antidote available for rivaroxaban[23].

Group II and III patients had significantly more hyperkalemic events during treatment than did the group I patients. It is known that nadroparin calcium treatment elevates serum potassium levels[24]. Group I and II patients also required additional potassium binder therapy.

Group I reported fewer other side effects compared to groups II and III. Nadroparin calcium treatment is known to cause injection site hematoma, skin rash, cutaneous necrosis, hematuria, leg weakness, numbness and purpura[25]. Rivaroxaban is generally well-tolerated compared to nadroparin calcium.

Rivaroxaban is an economical therapy compared to nadroparin calcium for DVTS following THR surgery[26]. The cost of therapy was lowest for group I, followed by group II. Previous studies have not considered economic aspects of rivaroxaban and nadroparin calcium use in the context of the Chinese healthcare system.

CONCLUSION

Rivaroxaban tablets (10 mg OD), low-dose nadroparin calcium (S/c OD) and high-dose nadroparin calcium (S/c OD) are effective treatments for DVTS following THR surgery, although there are side effects associated with each treatment. Rivaroxaban is more cost-effective than nadroparin calcium. Physicians are advised to use any of these therapies according to the patient's condition.

SIGNIFICANCE STATEMENTS

This study discovered the efficacy outcomes, adverse effects and the cost of therapy of rivaroxaban and nadroparin in a Chinese population that can be beneficial for the choice of therapy for anticoagulant prophylaxis treatment in the major surgery. This study will help the researcher to uncover the critical areas of selection of anticoagulant in the prevention of venous thromboembolism following major surgery that many surgeons are not able to discover.

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