

Efficacy and Safety Study of Low-Molecular-Weight Heparin and Fondaparinux Sodium After Hip Arthroplasty: A Retrospective Cohort Study

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Background: Low molecular heparin(LMWH) and sodium sulfadiazine heparin(FPX) are commonly used to prevent deep vein thrombosis(DVT) after total hip arthroplasty(THA). In this study, we compared the role of these drugs in preventing DVT after THA.

Methods: Patients who underwent unilateral THA at the Sixth Affiliated Hospital of Xinjiang Medical University from April 2020 to December 2022 were retrospectively analyzed for inclusion in this study. According to the anticoagulant drugs used, the patients were divided into LMWH group (n=106) and FPX group (n=97). Changes in perioperative coagulation-related indices, hemoglobin, blood loss And the postoperative complications.

Results: The preoperative indexes of the two groups of patients, the difference was not statistically significant ($P>0.05$); the indexes of Intraoperative blood loss, Visible blood loss, Hidden blood loss, and Total blood loss of the two groups of patients were compared, and the difference was not significant ($P>0.05$); PT activity and INR in the LMWH group were significantly lower than those in the FPX group on the 1st and 5th postoperative days, and the differences were significant ($P<0.05$); Platelets, Hemoglobin, Hematocrit, D-dimer, and Fibrinogen were compared between the two groups on the 1st and 5th postoperative days, and the differences were not significant ($P<0.05$). The differences were not significant ($P>0.05$). The differences in blood transfusion rate and blood volume between the two groups were not significant ($P>0.05$); the total hospitalization cost of the LMWH group was significantly lower than that of the FPX group, and the difference was significant ($P<0.05$); and the differences in the incidence of postoperative complications between the two groups were not significant ($P>0.05$).

Conclusion: In this study, we found that the efficacy and safety of FPX and LMWH in preventing VTE after THA were basically the same, and the total cost of hospitalization in the LMWH group was significantly lower than that in the FPX group; however, due to the limited inclusion of the sample size, high-quality, large-sample, long-term follow-up clinical studies are necessary.

Keywords: hip osteoarthritis, total Hip arthroplasty, low-molecular-weight heparin, fondaparinux sodium, coagulation indicator, thrombosis

Background

As the population lives longer, the number of patients with osteoarthritis increases, so does the number of patients treated with artificial joint replacement.^{1,2} Total hip arthroplasty (THA) is one of the most popular treatments for the hip. Total hip arthroplasty (THA) is currently an effective treatment for hip diseases.³ Deep vein thrombosis (DVT) is a disease of impaired venous return caused by abnormal clotting of blood in deep veins, which is a serious complication after total hip arthroplasty (THA), affecting the recovery of joint function and even threatening the recovery of joint function.⁴ DVT is a serious complication after total hip arthroplasty (THA), affecting the restoration of joint function and even threatening life⁵ It is a serious complication after total hip arthroplasty (THA). Relevant literature reports⁶ The incidence of DVT

after THA can be as high as more than 50% if relevant preventive measures are not taken. Therefore, active and effective measures should be taken to reduce the incidence of DVT after THA to improve the prognosis of patients. Low molecular heparin (LMWH) and sodium pentoxifylline (FPX) are commonly used to prevent DVT after THA. However, data on the effects of both after TKA are still lacking. In this study, we compared the preventive effects of LMWH and FPX on lower extremity DVT after THA. Our findings may inform the selection of appropriate anticoagulation therapy after THA.

Methods

Patients and Design

This was a retrospective study approved by the Ethics Committee of the Sixth Affiliated Hospital of Xinjiang Medical University under the ethical approval number LFYLLSC20230618-01. All study subjects signed an informed consent form (Figure 1).

Based on recommendations in the literature, all LMWH groups in our trial received half of the normal dose of low molecular heparin calcium subcutaneously at 4–6 hours postoperatively. The normal dose was injected the next day (once daily). FPX group: a 2.5 mg dose was injected subcutaneously starting 6 hours postoperatively (once daily). The duration of treatment was 2 weeks. The choice of anticoagulant drugs was decided by the doctor and the patient after the consultation. Inclusion criteria: (1) age ≥ 18 years; (2) planned initial THA due to end-stage osteoarthritis or femoral head necrosis. (Figure 2 exclusion criteria: (1) revision or bilateral surgery; (2) history of previous ipsilateral hip surgery; (3) contraindications to the use of LMWH and FPX, allergy within 6 months or history of thrombosis; (4) preoperative anemia, hemoglobin (HB) levels, < 12 g/dl in women and < 13 g/dl in men; (5) body mass index > 35 kg/m²; (6) coagulation disorders.

Surgical Procedures and Postoperative Rehabilitation

All THAs were performed using a posterolateral approach by a surgical team of 2 senior orthopedic surgeons. General anesthesia and controlled hypotensive anesthesia (BP $< 100/60$ mmHg) were used. Uncemented acetabular prosthesis

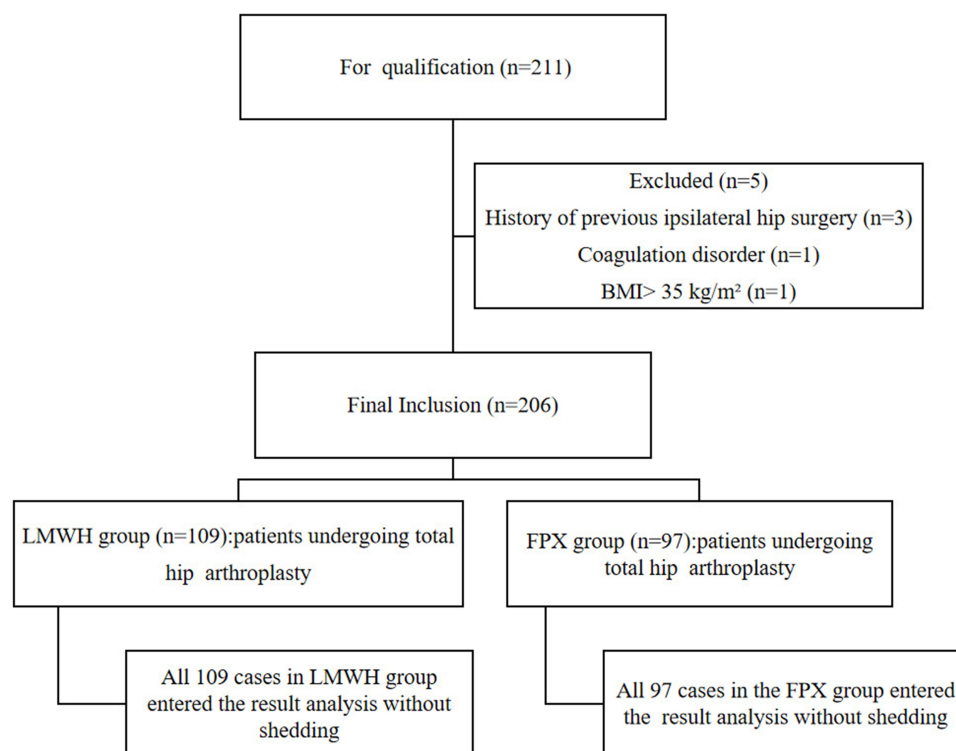


Figure 1 Patient flow chart.

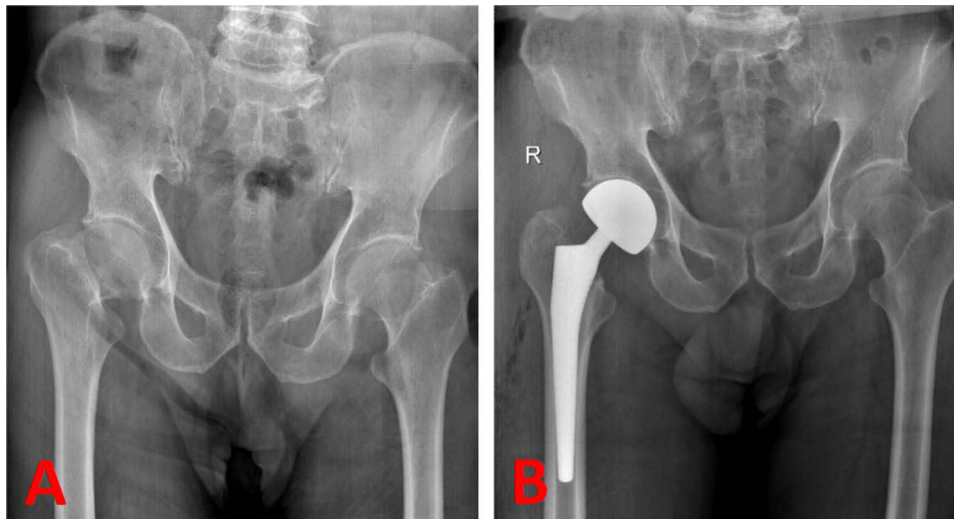


Figure 2 (A) Pre x-ray before right Hip arthroplasty; (B) The x-ray after right Hip arthroplasty.

(Johnson & Johnson Pinnacle acetabular prosthesis) and femoral stem (Johnson & Johnson Corail femoral stem) were used as conventional prostheses.

All patients were routinely given postoperative care and thromboprophylaxis before weight-bearing walking, and walking training and strength training were started on the first postoperative day. On the 1st, 3rd, 5th and 9th postoperative days, the physician in charge of the patient's incision cleaned with iodine povidone-iodine and observed the recovery of the incision, and if there was any abnormality, it was reported to the physician in time and was treated in a timely manner. On the 7th postoperative day, the patient received ultrasound examination of both lower limbs; the sutures were routinely removed on the 12th postoperative day, but if the patient had complications such as necrosis of the skin edge of the incision or fat liquefaction, the physician in charge had to report to the supervising physician, and the sutures could not be removed until the incision had completely healed. After discharge, patients were told to come to the hospital for regular follow-up of B ultrasound of lower limb blood vessels and coagulation function in 1 or 2 months after the operation; during this period, patients were required to stay in bed strictly, and were not allowed to go down to the ground for weight bearing. Rivaroxaban (Bayeritol, 10 mg, Bayer AG) was administered orally to prevent thrombosis for 15 d. Doppler ultrasound was routinely used to detect deep vein thrombosis at the time of discharge from the hospital, at the 1-month follow-up, or when deep vein thrombosis (DVT) was suspected. If necessary, chest CT-PA was used to detect pulmonary embolism. Blood transfusion protocols were used for patients with hemoglobin levels below 70 g/L, or hemoglobin values of 70–100 g/L accompanied by anemia-related symptoms such as dizziness, palpitations, shortness of breath, or decreased exercise tolerance.

Ending Indicator

The demographic characteristics and medical history of the patients were recorded preoperatively.

Main Outcome Indicators

The main outcome indicators were Platelets, Hemoglobin, Hematocrit, D-dimer, PT activity, INR, Fibrinogen, and estimated blood loss (EBL), overt blood loss, occult blood loss, transfusion rate, transfusion volume, and blood test on the 1st and 5th postoperative days. EBL, apparent blood loss, occult blood loss, transfusion rate, transfusion volume, and blood test. Total blood loss was calculated according to the Gross equation and Nadler equation method: total blood volume= $k_1 \times \text{height (m)}^3 + k_2 \times \text{weight (kg)} + k_3$, of which the coefficients for men were $k_1=0.3669$, $k_2=0.03219$, and $k_3=0.6041$, and those for women were $k_1=0.3561$, $k_2=0.03308$, and $k_3=0.1833$. Total blood loss= $\text{blood volume} \times (\text{height (m)}^3 + k_2 \times \text{weight (kg)} + k_3)$. blood loss = blood volume \times (preoperative erythrocyte pressure volume - lowest postoperative erythrocyte pressure volume)/mean erythrocyte pressure volume, explicit blood loss was defined as intraoperative blood loss + volume of drainage, and implicit blood loss = total blood loss - explicit blood loss + volume of transfused erythrocytes.

Secondary Outcome Indicators

Postoperative length of stay, duration of surgery, total hospitalization costs and postoperative complications (interosseous vein thrombosis, deep vein thrombosis, pulmonary thrombosis, incisional infections and mortality).

Statistical Analysis

SPSS 26.0 software was used to statistically analyze the data. All results from measured data in this study are presented as mean \pm standard deviation, and categorical data are presented as percentages and frequency counts; since no major deviations from normality were detected, *t*-tests were used to compare continuous variables between the two treatment groups (LMWH and FPX groups), whereas comparisons of categorical variables were made using chi-square tests or Fisher's exact test.

Patient Demographics

A total of 206 patients (LMWH: 109, FPX: 97) who underwent total hip arthroplasty were collected in this study. The baseline characteristics of the two groups were comparable and are summarized in [Table 1](#)

Comparison of Preoperative Data Between the Two Groups

Preoperative age, gender composition, body mass index, surgical site, hypertension, diabetes mellitus, coronary heart disease, neurological disease, respiratory disease, metabolic disease, as well as platelets, hemoglobin, erythrocyte pressure volume, D-dimer, plasminogen activity (PT), the internationalized standard ratio, and fibrinogen of the patients in the two groups were compared, and the differences were not significant ($P > 0.05$), as shown in [Table 1](#)

Comparison of Perioperative Bleeding Between the Two Groups

Intraoperative blood loss, Visible blood loss, Hidden blood loss, and Total blood loss were compared between the two groups, and the differences were not significant ($P > 0.05$), as shown in [Table 2](#).

Table 1 Comparison of the Preoperative General Data Between the Two Groups

Index	FPX (n=97)	LMWH (n=109)	t	P
Age(y, $\bar{X} \pm S$)	77.17 \pm 5.48	76.27 \pm 5.06	1.244	0.222
Sex (n, Male/Female)	36/61	39/70	0.039	0.843
BMI (kg/m ² , $\bar{X} \pm S$)	23.76 \pm 4.03	23.51 \pm 3.54	0.474	0.636
Position (Left/Right)	39/58	53/56	1.471	0.225
Basic disease (n)				
Hypertension	43	52	0.235	0.627
Diabetes	27	41	2.220	0.136
Cardiovascular system	39	45	0.025	0.875
Nervous system	23	32	0.836	0.361
Respiratory system	12	13	0.010	0.922
Osteoporosis	22	29	0.424	0.515
Preoperative values				
Platelets (10 ¹² /L)	214.54 \pm 84.96	206.78 \pm 73.57	0.702	0.483
Hemoglobin (g/L)	121.35 \pm 20.73	116.18 \pm 22.17	1.721	0.087
Hematocrit (%)	36.35 \pm 5.99	35.38 \pm 5.99	1.168	0.244
D-dimer (mg/L)	9.17 \pm 11.02	8.47 \pm 10.13	0.476	0.635
PT activity (%)	104.34 \pm 17.49	103.40 \pm 16.10	0.403	0.687
INR	1.03 \pm 0.14	1.06 \pm 0.12	-1.441	0.151
Fibrinogen	3.64 \pm 1.22	3.91 \pm 1.17	-1.629	0.105

Notes: The continuous value was given as the mean and the standard deviation. Body mass index=weight/height². $\bar{X} \pm S$: mean \pm standard deviation; n: sample size.

Abbreviation: INR, International normalized ratio.

Table 2 Comparison of Perioperative Blood Loss Between the Two Groups

Index	FPX (n=97)	LMWH (n=109)	t	p
Intraoperative blood loss (mL)	190.10±155.74	216.88±163.79	-1.199	0.232
Visible blood loss (mL)	190.61±155.35	216.88±163.79	-1.177	0.241
Hidden blood loss (mL)	782.48±745.36	587.37±679.36	1.966	0.051
Total blood loss (mL)	746.30±731.14	605.17±699.26	1.415	0.159

Notes: The continuous value was given as the mean and the standard deviation.

Abbreviation: mL, milliliter.

Comparison of Postoperative Coagulation Indices Between the Two Groups

The PT activity and INR of the LMWH group were significantly lower than those of the FPX group on the 1st and 5th postoperative days, and the differences were significant ($P < 0.05$), See Figures 3 and 4. the differences in the ratios of Platelets, Hemoglobin, Hematocrit, D-dimer, and Fibrinogen on the 1st and 5th postoperative days of the patients in the two groups were not significant ($P > 0.05$). significance ($P > 0.05$). See Table 3 and 4.

Comparison of Blood Transfusion Rate and Volume Between the Two Groups

In the FPX group, there were 42 transfusion cases in the perioperative period, with a transfusion rate of 43.3% and a volume of (253.60±340.97) mL; in the LMWH group, there were 38 patients who were transfused, with a transfusion rate of 34.9% and a volume of (203.66±347.45) mL; the difference in the rate of transfusion and the volume of transfusion in these two groups was not significant ($\chi^2 = 1.538$, $\chi^2 = 1.039$, $p > 0.05$). See Table 5.

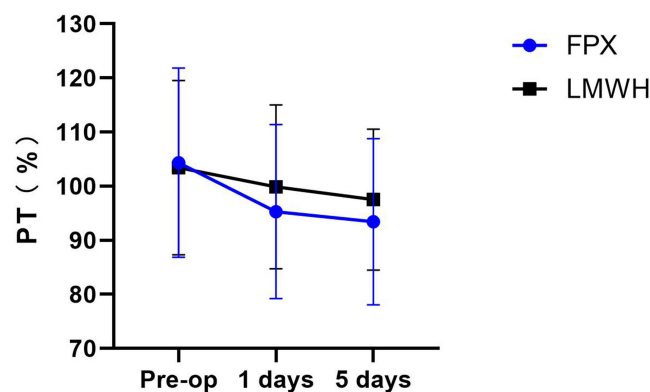


Figure 3 Comparison of the first, postoperative day and fifth postoperative day after PT activity surgery.

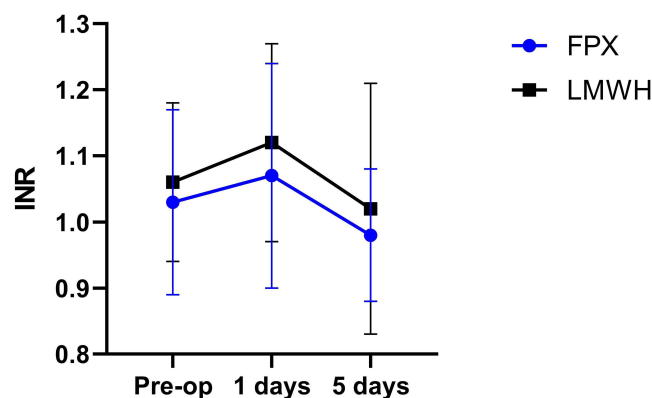


Figure 4 Comparison of the first, postoperative day and fifth postoperative day after INR surgery.

Table 3 Comparison of the Coagulation Tests on Day 1 After Surgery

Variable	FPX (n=97)	LMWH (n=109)	t	p
Platelets (10^{12} /L)	259.70±90.45	262.32±86.66	-0.212	0.832
Hemoglobin (g/L)	100.25±16.52	100.52±16.29	-0.118	0.906
Hematocrit (%)	30.24±4.81	30.99±4.34	-1.180	0.239
D-dimer (mg/L)	5.20±4.67	6.59±5.52	-1.960	0.051
PT activity (%)	95.29 ± 16.06	99.87 ± 15.13	-2.099	0.037*
INR	1.07 ± 0.17	1.12 ± 0.15	-2.166	0.031*
Fibrinogen	4.77±1.25	4.61±1.06	0.980	0.328

Notes: The continuous value was given as the mean and the standard deviation. *Indicates statistically significant difference between the two groups ($P < 0.05$).

Abbreviation: INR, International normalized ratio.

Table 4 Comparison of the Coagulation Tests on Day 5 After Surgery

Variable	FPX (n=97)	LMWH (n=109)	t	p
Platelets (10^{12} /L)	300.23±112.80	295.96±93.27	0.296	0.768
Hemoglobin (g/L)	100.52±18.83	97.22±14.69	1.403	0.162
Hematocrit (%)	30.20±4.44	30.07±4.20	0.207	0.836
D-dimer (mg/L)	4.65±2.65	5.13±2.65	-1.283	0.201
PT activity (%)	93.42 ± 15.33	97.50 ± 13.04	-2.066	0.040*
INR	0.98 ± 0.10	1.02 ± 0.19	-2.056	0.041*
Fibrinogen	5.15±1.31	4.99±1.08	0.948	0.345

Notes: The continuous value was given as the mean and the standard deviation. *Indicates statistically significant difference between the two groups ($P < 0.05$).

Abbreviation: INR, International normalized ratio.

Table 5 Postoperative Hospital Stay and Complications in the Rate of Transfusion and the Volume of Transfusion in Both Groups

groups	n	Blood Transfusion Rate (n/%)	Blood Transfusion
FPX	97	42/43.3	253.60±340.97
LMWH	109	38/34.9	203.66±347.45
t		1.538	1.039
p		0.215	0.300

Notes: The continuous value was given as the mean and the standard deviation.

Comparison of Secondary Outcome Indicators

Total hospitalization costs were significantly lower in the LMWH group than in the FPX group, and the difference was significant ($P < 0.05$);

Compared with the hospitalization time and operation time in the two groups, the difference was not significant ($t=0.543$, $t=0.303$, $P > 0.05$). Comparison of the incidence of various postoperative complications between the two groups was not significant ($\chi^2=0.134$, 0.981 , 2.269 , 1.129 , $P > 0.05$), as shown in Table 6. There were no critical complications such as pulmonary thrombosis, acute renal failure or epilepsy, or death in the postoperative period of the two groups, which indicates that the two drugs are basically the same in terms of their safety for the organism. See Table 6.

Discussion

Total hip arthroplasty (THA) is the primary intervention for the treatment of end-stage hip disease and plays a crucial role in improving the quality of life of elderly patients^{3,7,8}. In hip replacement patients, postoperative lower limb activity is limited and blood flow velocity decreases, leading to venous injury, venous stasis and hypercoagulability of blood³. This leads to

Table 6 Postoperative Hospital Stay and Complications in Both Groups with the Hospitalization Time and Operation Time

Variable	FPX (n=97)	LMWH (n=109)	t	p
LOH (day)	18.91±9.24	18.33±5.83	0.543	0.588
Operative time (min)	85.00±31.86	83.53±36.96	0.303	0.762
Expenses Δ	48,717.85±17,839.76	42,993.72±13,818.06	2.589	0.010*
Thromboembolic event (n, 100%)				
Interosseous vein thrombosis	38 (48.70)	40 (35.30)	0.134	0.714
Deep vein thrombosis	11 (42.30)	15 (57.70)	0.981	0.612
Pulmonary thrombosis	0 (0.00)	0 (0.00)	/	/
Cutaneous infection	2 (2.10)	0 (0.00)	2.269	0.132
Mortality rate	1 (1.00)	0 (0.00)	1.129	0.288

Notes: The continuous value was given as the mean and the standard deviation. Δ Results are presented in Chinese yuan.

*Indicates statistically significant difference between the two groups ($P < 0.05$).

Abbreviation: LOH, length of hospital stay.

frequent occurrence of adverse events such as postoperative DVT and pulmonary embolism, which are the main causes of mortality and morbidity after total hip arthroplasty.⁹ They are the main causes of mortality and morbidity after total hip arthroplasty. Prophylactic anticoagulation has become essential in the perioperative period of THA and has significantly reduced the overall incidence of postoperative venous thromboembolism (VTE)¹⁰. However, despite prophylactic anticoagulation, some patients continue to experience these serious complications during and after hospitalization¹¹.

Clinically, low molecular weight heparin, sodium sulfadiazepoxide, rivaroxaban, warfarin and other drugs are often used for early anticoagulant therapy for patients with hip arthroplasty, and all of them can achieve better results.^{12,13} Low molecular weight heparin is widely used in perioperative DVT prevention in orthopedic major surgery, belonging to the first-line anticoagulant drugs, which can effectively reduce the biological activity of activated coagulation factors, thus inhibiting platelet aggregation, inducing fibrinolysis, and achieving the purpose of removing venous thrombus embolus, and the drug has a longer half-life, with a good degree of utilization.¹⁴ The drug has a long half-life and good utilization. Fondaparinux sodium is a synthetic selective inhibitor of activated factor X. Its pentose structure significantly increases the affinity of antithrombin (AT), which specifically binds to the activation site of antithrombin through its non-covalent bond, resulting in the rapid inhibition of activated coagulation factor X, which in turn reduces the production of prothrombin and fibrin formation.^{15,16} This results in rapid inhibition of activated factor X, thereby reducing thrombin production and fibrin formation. Unlike UFH and LMWH, sodium sulfadiazepoxide is not expected to bind to platelet factor IV and does not cross-react with plasma from patients with heparin-induced thrombocytopenia.^{17,18} Sulfohepatidine sodium is not expected to bind to platelet factor IV or cross-react with plasma from patients with heparin-induced thrombocytopenia. Sodium sulfadoxine heparin has unique anticoagulant activity and a longer half-life (10 ~ 15 h) than LMWH. Low molecular weight heparin is a sulfated glycosaminoglycan salt with a molecular weight significantly greater than that of sodium sulfadiazepate¹⁹ Sulphated glycosaminoglycan salts. The average molecular weight of sodium sulfated heparin is below 8000 Da, and at least 60% of its molecular weight is distributed below 8000 Da.^{20,21} The average molecular weight of sulfadoxine sodium is below 8000 Da and at least 60% of the molecular weight is below 8000 Da. Because of its small molecular weight and monotonous action, sulfadoxine does not have many of the important pharmacological properties of pharmaceutical heparin, except for its specific binding to the anti-Xa factor.²² It does not have many of the important pharmacologic properties of pharmaceutical heparin. The present study showed that PT activity and INR indexes were significantly higher in the LMWH group than in the FPX group on postoperative days 1 and 5, ($t_{1\text{day}} = -3.096$, $t_{5\text{day}} = -2.648$, $P < 0.05$), indicating that the time of plasminogen activation was shortened in the FPX group, which made the formation of thrombus easier. This study also showed that the total cost of hospitalization was lower in the LMWH group than in the FPX group, suggesting that the cost of VTE prevention was lower in the LMWH group and therefore more economical to use.

Some studies have shown that²³ DVT is one of the common and major complications of THA. Without any preventive measures, the probability of lower extremity deep vein thrombosis (DVT) after hip arthroplasty is 39%-74%, and the probability of pulmonary artery embolism (PAE), which has a high lethality rate, is 0.5%-2%, and proximal

DVT is the main source of pulmonary embolism, which is the most important perioperative cause of orthopedic death.²⁴ Once pulmonary embolism occurs, the disease progresses rapidly, and the current treatment options are very limited and the prognosis is poor.¹³ In the present study, we found that two patients with pulmonary venous thrombosis (PVT) were found to have a high risk of pulmonary embolism. In this study, we found Intraoperative blood loss, Visible blood loss, Hidden blood loss, Total blood loss in two groups, There was no significant difference between the rates of blood transfusion and thromboembolic events. These results suggest that there is no significant difference in the incidence of DVT after TKA prevention with LMWH and FPX. Some studies have found that²⁵ the incidence of thrombocytopenia caused by LMWH is low. For patients with thrombocytopenia caused by FPX, LMWH can be replaced. Heparin inhibited adrenal aldosterone synthesis, occasionally causing hyperkalemia, and mild transaminase elevation by FPX.

Limitations of the Article

① This trial is a retrospective study, so there may be the possibility of loss of data or failure to record data in time, which may bias the results, but the research team to which the authors belonged strictly and carefully recorded the postoperative outcome indicators of each group to maximize the completeness of the experimental data; ② The sample size of the inclusion of the relatively small, statistically insufficient efficacy of the reporting of bias, and the results of this study need further, multicenter, prospective studies to further elucidate the relationship between clinical outcomes. The results of this study require further multicenter, prospective studies to further elucidate the relationship between clinical outcomes.

Conclusions

In conclusion, this study found that the efficacy and safety of FPX and LMWH in preventing VTE after THA were basically the same, and the total hospitalization cost of the LMWH group was significantly lower than that of the FPX group; however, due to the limited sample size included, high-quality, large-sample, long-term follow-up clinical studies are necessary.

Abbreviations

BMI, Body mass index; DVT, Deep vein thrombosis; Hb, Hemoglobin; Hct, Hematocrit; INR, International normalized ratio; THA, total hip arthroplasty; LMWH, low-molecular-weight heparin; LOH, length of hospital stay.

Data Sharing Statement

Follow-up regarding the Efficacy and safety study of low-molecular-weight heparin and fondaparinux sodium after hip arthroplasty: a retrospective cohort study is not complete, so the dataset analyzed in this study is not publicly available but is available to the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

We confirm that all experiments were performed in accordance with the Declaration of Helsinki. The study was approved by the Ethical Committee of the Xinjiang Medical University Affiliated Sixth Hospital, NO: LFYLLSC20230713-01. Each patient provided written informed consent before participating in the study.

Funding

There is no funding to report.

Disclosure

Abuduwupuer Haibier and Alimujiang Yusufu are co-first authors for this study. The authors report no conflicts of interest in this work.

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