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Original Article

A Comparison Between Fondaparinux Sodium and Low-Molecular-Weight Heparin in Preventing Patients Undergoing Hip Replacement from Deep Vein Thrombosis

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Abstract

Objectives: Total hip arthroplasty (THA) is a highly successful and effective surgery for improving hip functions and relieving pain. However, the lower extremities are prone to deep vein thrombosis (DVT) and swelling after surgery, thereby delaying recovery. In this study, we investigated the preventive effects of fondaparinux sodium (FS) and low-molecular-weight heparin (LMWH) on DVT of the lower extremity after THA. **Methods**: Firstly, 60 patients who underwent THA at the First Affiliated Hospital of Wannan Medical College from March 2020 to December 2020 were included. Next, the patients were randomly divided into an LMWH group (n = 30) and an FS group (n = 30). Then, the indexes related to DVT were compared between both groups. **Results**: Specifically, the differences in baseline data, such as age, gender and body mass index (BMI), between the two groups were not statistically significant. The postoperative weight bearing time of patients in the FS group was much shorter than that in the LMWH group. **Conclusion**: Subcutaneous injection of FS not only exhibits superior effects to LMWH in preventing DVT after THA but also has a correlation with reducing the risk of thrombosis and improving patient symptoms.

Keywords: Deep Vein Thrombosis, Fondaparinux Sodium, Low-Molecular-Weight Heparin, Preventive Effect, Total Hip Arthroplasty

Introduction

As reported by National Bureau of Statistics, China had 209 million people aged ≥ 65 years old by the end of 2022, accounting for 14.9% of the total population, and this percentage is predicted to be 14% in 2025 and about 30% by 2050[1, 2]. Hip fracture is the second leading fracture type in the older population in China, accompanied with as high as 20–30% of one-year mortality rate[3,4]. Once hip fracture occurs, the hip function and walking ability of patients are severely restricted, leading to a lower quality of life. Currently, surgery is an effective way to treat hip fractures. The effective surgeries for hip fractures mainly consist of hip hemiarthroplasty (replacement of the femoral head with a prosthesis) and total hip arthroplasty (THA, replacement of the femoral head and acetabulum with a prosthesis)[5]. However, the instability of the end of the fracture usually results in fracture nonunion. Additional, relative to hemiarthroplasty, THA exhibits better functional outcomes and lowest rate of additional procedures, revealed by a number of randomized controlled trials (RCTs)[6]. However, perioperative hemoglobin (Hb) can be severely reduced by the intraoperative release of hip capsule, synovium and soft tissue excision, and femoral neck osteotomy[6,7]. Further, deep vein thrombosis (DVT) of lower limbs and pulmonary embolism, the common complications after hip replacement, usually result in slow recovery and even poor surgical outcomes[8]. Therefore, we believe it useful to identify an easy-to-obtain and efficient drug to reduce the occurrence of postoperative DVT in the limbs and optimize the enhanced recovery after surgery (ERAS) protocols.

Despite serving as a reliable anticoagulant most widely

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used in the prevention and treatment of DVT, low-molecular-weight heparin (LMWH) is also associated with some adverse events such as subcutaneous congestion and local sclerosis[9]. Fondaparinux sodium (FS), a novel antithrombotic agent used in patients undergoing hip replacement, has been shown to effectively prevent venous thromboembolic events[10]. In addition, FS has no correlation with inhibition of the platelet-activating factor; thus, it might not lead to a hemorrhage reaction. However, there is a lack of studies on the comparison between FS and LMWH in preventing DVT after THA. Therefore, this study was designed to investigate the preventive effects of FS and LMWH on DVT induced by THA. Overall, this study could be used as clinical treatment guidance for improving the postoperative outcomes of THA.

Materials and Methods

Clinical Data

A total of 60 patients who underwent THA from March 2020 to May 2020 at the First Affiliated Hospital of Wannan Medical College were selected and randomly divided into two groups in a 1:1 ratio. Two assignment sequences (LMWH group and FS group, n = 30) were generated by computer randomization by a nurse who was not involved in patient registration and treatment. The assignment results were placed in an envelope then distributed to the patients participating in the study. The envelope was opened after surgery and the patient was given appropriate treatments according to the assigned sequence. The two groups were named as LMWH group (n = 30) and FS group (n = 30) according to the antithrombotic agents used after surgery, and the general information of all patients was collected. Besides, the informed consent was signed by all enrolled patients, and this study was approved by the Ethics Committee of the First Affiliated Hospital of Wannan Medical College.

The inclusion criteria were as follows: (1) conservative treatment was ineffective, and patients suffered from severe pain; (2) age: 30–85 years; (3) without previous history of THA; (4) cerebral infarction and DVT of both lower limbs. The exclusion criteria consisted of (1) a body mass index (BMI) >30 kg/m^2; (2) presence of a recent infection; (3) coagulation disorders and recent use of anticoagulants; (4) a history of cerebral infarction.

Surgical Procedure

Preoperative preparation: The affected limb function, cardiopulmonary function, liver and kidney function, anticoagulant function, inflammatory indicators and blood vessels of both lower limbs were assessed to confirm that there were no contraindications for surgery. Then, Cefazolin Sodium (2.0 g) was intravenously dripped 30 min before surgery for preventive anti-infection treatment.

Surgical methods: All operations were performed by the same group of doctors. Firstly, patients were given general and nerve block anesthesia. Next, a standard posterolateral incision was made to expose the hip capsule and remove the joint capsule and synovial membrane. The hip joint was rotated externally and adducted to dislocate the femoral head. Then, the femoral head was resected, the femoral neck was repaired, and the medullary cavity was enlarged. Subsequently, the labrum of the joint was removed, the round ligament, all soft tissue in the acetabulum and cartilage surface, and the acetabulum were exposed and cleaned. After that, the artificial acetabulum was placed, and the artificial femoral head was replaced. Upon a satisfactory test, the wound was subject to pulse flushing with a large amount of physiological saline, sutured by layers, and covered with pressure. Intravenous drops of 0.8 g of Tranexamic acid were given before and during surgery.

Postoperative Management

After returning to the ward, the patient received t-shoe fixation and intermittent pneumatic compression therapy. Half an hour later, intravenous analgesia with flurbiprofen ester was performed, followed by passive flexion and extension exercises of the toe and ankle joints. Celecoxib combined with tramadol for oral analgesia was administered on the second day after surgery. Cefazolin Sodium was routinely used for anti-infection treatment and anticoagulant treatment. The medical staff encouraged and guided functional exercises of the hip joint on the second day after surgery. Besides, conventional anteroposterior and lateral radiographs of both hips were acquired. The blood routine indexes were normal three days after surgery, the body temperature was normal, and the incision healing was good; the swelling of the affected limb subsided seven days after surgery. Finally, the patients who reached the above conditions were discharged.

Use of Fondaparinux Sodium (FS) and Low-Molecular-Weight Heparin (LMWH)

Patients in both groups received drug administration from the 1st day after surgery. Patients in the FS group was subcutaneously injected with 4000 IU FS, while those in the LMWH group was subcutaneously injected with 4000 IU LMWH, both once a day. None of patients were informed which group they assigned.

Outcome measures

The outcome measures were assessed and collected by a single researcher who was not aware of the interventions. The baseline data of patients, including age, gender, BMI, were recorded. Besides, the operation time and postoperative weight bearing time were measured; DVT rate, subcutaneous extravasation, visual analogue scale (VAS) score and Wells score were recorded on the days 3, 5, and 7 after surgery. The difference in swelling circumference was estimated by measuring the circumference 10 cm away from the upward side of the patella, which was recorded at days 3, 5 and 7 days after surgery.

Figure 1. Preoperative (left) and postoperative (right) X-ray images of THA patients.

Table 1. Baseline demographic and clinical characteristics.

Characteristics	FS group (n = 30)	LMWH group (n = 30)	*P* value
Gender, n (%)			
Male	10 (33.3)	14 (46.7)	0.054
Female	20 (66.7)	16 (53.3)	
Age, year, mean ± SD	71±2.128	70.3±1.714	0.167
Hypertension, n (%)	5 (16.7)	6 (20)	0.547
Hyperlipidemia, n (%)	3 (10)	5 (16.7)	0.164

LMWH, Low-molecular-weight heparin calcium; FS, Fondaparinux sodium.

The pain degree was quantified into 0–10 points by VAS. Based on this, the pain experienced by the patients was scored[11]. Specifically, 0 point represented no pain, 3 points represented mild pain (could be tolerated), 4–6 points represented pain and sleep disorders, and 7–10 points represented progressively intense pain that became unbearable.

We assessed the likelihood of pulmonary embolism based on the clinical features and history of patients. A Wells score of 0–1 indicated a low risk, 2–6 indicated a moderate risk, and a score > 6 indicated a high risk of pulmonary embolism[12].

Statistical Analysis

SPSS V17.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. Quantitative data were normally distributed and presented as mean ± standard deviation (SD); the difference between two groups was assessed using unpaired Student's *t*-test, and Cohen's d was calculated. Categorical data were presented as n (%); a chi-square test was used to compare the differences between two groups, and chi-square values were provided. $P < 0.05$ indicated a statistical significance.

Results

Baseline Data

A total of 60 patients who received THA were randomly divided into two groups (FS group and LMWH group). As shown in Table 1, the baseline demographic and clinical characteristics of patients from both groups were similar. No significant differences were observed in age (P = 0.167), gender (P = 0.054), hypertension (P = 0.547) and hyperlipidemia (P = 0.164) between two groups of patients. X-ray images of THA patients before and after surgery were shown in Figure 1.

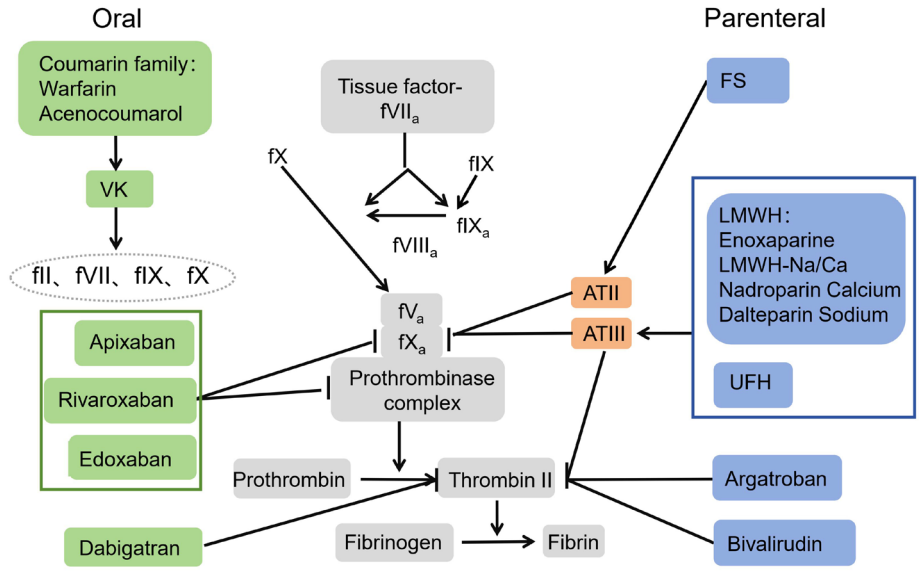

Figure 2. The mechanism of anticoagulant effect of different anticoagulants. UFS, unfractionated heparin; VK, Vitamin K.

Table 2. Comparison of operation time and postoperative weight bearing time between the two groups (mean ± SD).

Characteristics	FS group (n = 30)	LMWH group (n = 30)	*P* value	Cohen's d
Operation time, min	86.07±4.118	85.8±3.773	0.795	0.521
Postoperative weight bearing time, day	2.433±1.006	3.00±1.114	0.043	4.068

LMWH, Low-molecular-weight heparin calcium; FS, Fondaparinux sodium.

Comparison of Operation Time and Postoperative Weight Bearing Time Between the Two Groups

The operation time and postoperative weight bearing time of patients in the two groups were compared, and the results showed that the postoperative weight bearing time of patients in the FS group was significantly shorter than that in the LMWH group (2.433 ± 1.006 vs. 3.00 ± 1.114; *P* = 0.043, Cohen's d = 4.068). In addition, the operation time between the two groups was observed to be well balanced (*P* = 0.795, Cohen's d = 0.521) (Table 2).

Comparison of Related Indexes of DVT Between the Two Groups

Here, the indexes related to DVT of both lower limbs in the two groups were compared on the 3rd, 5th and 7th days after surgery (Table 3). The results showed that there were no statistically significant differences in DVT, Wells scores, subcutaneous ecchymosis, circumference of distinct difference analysis and VAS scores between the FS group and LMWH group on the 3rd and 5th days after surgery. However, on the 7th day after surgery, the FS group patients showed much lower DVT (3.3% vs. 13.3%, *P* = 0.01), Wells scores (7.133 ± 2.013 vs. 8.4 ± 1.192, *P* = 0.004, Cohen's d = 5.833), subcutaneous ecchymosis (3.3% vs. 20%, *P* = 0.000), difference in swelling circumference (50.23 ± 1.278 vs. 51.13 ± 0.9371, *P* = 0.003, Cohen's d = 6.117) and VAS scores (3.633 ± 1.189 vs. 4.267 ± 1.081, *P* = 0.035, Cohen's d = 3.153) than the LMWH group patients.

Discussion

Currently, THA is the most effective surgical treatment for patients with advanced aseptic osteonecrosis of the femoral head and femoral neck fracture. More importantly, THA is associated with alleviating hip pain and effectively restoring hip stability and functions[13]. Moreover, THA can also bring better functional outcomes, cause fewer wound infections, and reduce secondary procedure need[14]. However, DVT

Table 3. Comparison of related indexes of DVT of both lower limbs between two groups.

Characteristics	FS group (n = 30)	LMWH group (n = 30)	*P* value	Cohen's d / Chi-Square
Third				
DVT, n, (%)	4 (13.3%)	6 (20%)	0.204	1.617
Wells scores	13.13±1.408	13.57±1.331	0.226	2.446
Subcutaneous ecchymosis, n (%)	4 (13.3%)	7 (23.3%)	0.067	3.344
Swelling circumference, cm	51.5±1.324	52.27±2.803	0.219	2.675
VAS scores	4.5±1.432	4.6±1.276	0.776	0.562
Fifth				
DVT, n (%)	4 (13.3%)	6 (20%)	0.204	1.617
Wells scores	10.33±1.626	11.17±1.642	0.053	3.915
Subcutaneous ecchymosis, n (%)	4 (13.3%)	7 (23.3%)	0.067	3.344
Swelling circumference, cm	51.07±1.68	51.7±1.442	0.123	3.065
VAS scores	4.2±1.324	4.567±1.223	0.269	2.193
Seventh				
DVT, n (%)	1 (3.3%)	4 (13.3%)	0.010*	6.569
Wells scores	7.133±2.013	8.4±1.192	0.004*	5.833
Subcutaneous ecchymosis, n (%)	1 (3.3%)	6 (20%)	0.000*	13.548
Swelling circumference, cm	50.23±1.278	51.13±0.9371	0.003*	6.117
VAS scores	3.633±1.189	4.267±1.081	0.035*	3.153

P < 0.05; VAS scores, visual analogue scale; DVT, deep venous thrombosis; FDR, false discovery rate; LMWH, Low-molecular-weight heparin calcium; FS, Fondaparinux sodium.

and swelling, common complications after THA, result in delayed recovery, and may even threaten patients' lives. Anticoagulation therapy is the basis for the prevention and treatment of thrombosis[15]. The anticoagulants currently used for anticoagulation therapy include vitamin K antagonists (such as warfarin), novel direct oral anticoagulants (such as dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban), heparins (such as heparin, LMWH), and FS, all with various anticoagulant mechanisms (Figure 2)[16,17]. In this study, attention was mainly paid to the effect of FS and LMWH on postoperative DVT reduction and postoperative rehabilitation[18].

Since the introduction of ERAS in 2007, the concept of ERAS has been rapidly promoted in China. Recently, ERAS has been employed in THA, which not only reduces the length of hospitalization but also down-regulates postoperative complications and economic burdens on patients and their families[19]. However, early functional exercise of patients is mainly limited by factors such as the formation of DVT of the hip joint as well as swelling and pain in the affected limbs. Thus, it is extremely urgent to find effective and safe drugs to prevent DVT and achieve early functional exercises. Interestingly, this study showed that on the first day of DVT, the swelling level of the hip joint between the two groups was not significantly different. On the third and fifth days, there was no change in the occurrence of DVT and circumference in both LMWH and FS groups[20]. However, on the seventh day, the above indexes in the FS group were higher than those in the LMWH group. In another word, the incidence of DVT and the degree of limb swelling were relieved, which may be related to the subcutaneous injection of FS.

At present, THA has been widely used in clinical practice in China. Long-term anesthesia can slow blood flow, induce hypercoagulability, cause changes in the tunica intima of veins, and then increase the risk of venous thrombosis[21]. Routine postoperative anticoagulation therapy with FS and LMWH can effectively prevent DVT and reduce complications such as limb swelling, which is consistent with our research results. LMWH mainly exerts an anticoagulant effect through antithrombin III. After forming a complex with AT III, Xa activity acts as a selective depressant and slightly inhibits the II A and other coagulation factors, without affecting the formed thrombin. In the clinical application of heparin, the most common complication is heparin-induced thrombocytopenia and subcutaneous hemorrhage. Long-term application of heparin may increase the risk of thrombosis due to the depletion of antithrombin III and affect postoperative recovery due to injection pain, infection caused by subcutaneous injection or intolerance. FS is a chemically synthetic selective factor Xa inhibitor. The reversible binding of pentose structure induces the formation of factor Xa and indirectly inhibits the formation of thrombin and the enlargement of thrombus. However, FS does not affect the inhibition of AT on thrombin factor IIa nor the tissue factor

pathway inhibitors[22,23]. Similarly, FS does neither interact with platelets nor affect bleeding time. A clinical study has revealed that prophylactic use of FS reduces the risk of DVT in patients receiving THA[24]. In addition, FS is characterized with some advantages such as chemical nature of synthesis, minimal risk of contamination, 100% absolute bioavailability subcutaneously, instant onset of action, a long half-life, direct renal excretion, and fewer adverse reactions relative to direct oral anticoagulants. Furthermore, FS is an ideal alternative in conditions where oral anticoagulants are not approved for use in patients intolerant to LMWH[25].

Although FS, at approximately $85, is more expensive than LMWH, in practice FS is simple to administer (given at a fixed dose), does not require coagulation monitoring, and is effective in reducing the incidence of subcutaneous hemorrhage and D-dimer generation in clinical practice[26]. According to a cost-effectiveness analysis, FS offers an attractive economic alternative to initial DVT therapy that may result in cost savings without compromising clinical outcomes or patient safety[27]. Therefore, we believe that FS can provide beneficial costs to benefit the patients. In this research, the effects of FS on postoperative DVT of affected limbs were shown to be superior to LMWH, accompanied with a higher total effective rate and fewer adverse reactions. All in all, FS treatment is of great significance to the rehabilitation of patients.

This study confirmed that FS treatment had a better effect on postoperative rehabilitation of THA patients than LMWH in terms of operation time, postoperative weight bearing time, swelling, etc. However, laboratory indicators related to coagulation, including D-dimer, prothrombin time, activated partial thromboplastin time, etc., were not measured in THA patients before and after FS and LMWH treatment in this study. Hence, the detection of coagulation-related indicators will be further performed in future studies to more comprehensively evaluate the effects of different anticoagulants on postoperative DVT in patients.

Conclusion

Taken together, FS can not only effectively reduce the risk of DVT and the swelling degree of affected limbs in THA patients, but also shorten recovery time, facilitate early functional exercise and improve the degree of surgical satisfaction of patients.

Ethics approval

This study was approved by the Ethics Committee of Yijishan hospital.

Consent to participate

All patients provided signed informed consent.

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Author Contributions

Lin Wang is responsible for the study design. Lin Zhang and Zhujun Xu collected and analyzed the data. All authors participate in the manuscript writing and revising. All authors read and approved the final manuscript.

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