

The Efficacy of Low Molecular Weight Heparin for the Prevention of Venous Thromboembolism after Hip Fracture Surgery in Korean Patients

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Purpose: The aim of this study was to investigate the efficacy of low-molecular-weight heparin (LMWH) for the prevention of venous thromboembolism in Korean patients who underwent hip fracture surgery (HFS).

Materials and Methods: Prospectively, a total 181 cases were classified into the LMWH user group (116 cases) and LMWH non-user group (65 cases). Each group was sub-classified according to fracture types as follows: 81 cases of intertrochanteric fracture (group A: 49, group B: 32) and 100 cases of neck fracture (group C: 67, group D: 33). We compared the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) according to LMWH use.

Results: Of the 181 cases, four DVTs were found in the LMWH user groups (1 in group A, and 3 in group C). One case of PE was found in LMWH non-user group D. The incidences of DVT and PE showed no statistically significant differences between the LMWH user and non-user groups ($p=0.298$ and 0.359 , respectively). In subgroup analysis, no statistically significant differences were found between groups A and B and between groups C and D.

Conclusion: The administration of LMWH was not effective in the prevention of venous thromboembolism and PE in the Korean patients who underwent HFS.

Key Words: Low molecular weight heparin, deep vein thrombosis, pulmonary embolism, hip fracture

INTRODUCTION

Hip fractures mostly occur from falls among patients of older age, and are known to cause complications, such as pneumonia, pressure sore, sepsis, infections in the urinary system, and deep vein thrombosis (DVT). Among these, DVT is a major complication that can lead to pulmonary embolism (PE) and even death.

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Thrombosis has been reported to occur in more than 40% of hip fracture cases, and PE in 11%.¹⁻³ However, a study on the incidence of DVT after hip fracture among Koreans reported incidences of 3.5% for those with symptoms⁴ and 11.3% for those without symptoms,⁵ indicating a difference in incidence rates from those in studies conducted in Western populations.⁶ Moreover, reports have indicated that aspirin is effective in preventing venous thromboembolism (VTE) in Western patients, but is not as effective in Koreans.⁴ As such, the authors investigated the efficacy of low molecular weight heparin (LMWH) for the prevention of VTE in Korean patients who underwent hip fracture surgery (HFS).

MATERIALS AND METHODS

All procedures were approved by the Institutional Review Board of our institution. Between October 1, 2011 and Octo-

ber 1, 2013, 308 patients were admitted to our hospital, because of femur intertrochanteric or neck fractures. Among these patients, 26 did not undergo surgery, 66 received antiplatelet drugs for a cerebrovascular or cardiovascular disease, one was diagnosed with varicose vein, one had malignant tumor, six had chronic heart failure, seven had a platelet shortage (number of platelet $<100 \times 10^3 / \mu\text{L}$), and 20 did not undergo Doppler ultrasonography; these were excluded from the study. The remaining 181 patients were enrolled for analysis (Fig. 1). Randomly selecting patients who had visited the hospital during odd-number weeks, LMWH was administered.

In the LMWH user group, patients were administered 2500 IU of LMWH via subcutaneous injection of 2500 IU of LMWH within 8 hours from their arrival at the recovery room after operation. After which, they were administered LMWH once a day until 10 days after surgery. After discharge, a low dose of aspirin (100 mg) was administered up to 35 days after operation. Other pharmacological or physical methods to prevent VTE were not used.

In the patients who had no symptoms of VTE, we routinely checked for the possible occurrence of DVT at 10 days after surgery. A radiologist used Doppler ultrasonography, and selectively checked the proximal or distal vein and deep or superficial vein for possible occurrence of DVT. Acute lesions confirmed by the radiologist were included. In patients with clinically suspected VTE, Doppler ultrasonography was used even at less than 10 days after surgery. For patients with clinically suspected PE, computer tomographic (CT) pulmonary angiography was performed. To analyze symptoms known to be directly related to a bleeding tendency, we investigated whether the patient had any melena, hematuria, nasal bleeding, hematoma, bleeding in the injured area, and re-operation due to bleeding or thrombocytopenia (platelet count $<100 \times 10^3 / \mu\text{L}$). After discharge, the patients were routinely followed up at 6 weeks, 3

months, 6 months, and 12 months after the operation with a specific interview regarding VTE and bleeding tendency related complications. Patients who were not scheduled for follow-up visits were contacted by telephone.

Statistical analysis

For statistical analysis of the measured data, PASW statistics 18 (SPSS Inc., Chicago, IL, USA) was used. The statistical significance of the difference was determined by using Student’s t-test for continuous variables and the chi-square test for categorical variables. A *p* value ≤ 0.05 was considered significant.

RESULTS

Of the 181 patients evaluated, 116 were LMWH users and 65 were LMWH non users. The demographic data of each group are presented in Table 1. In order to analyze the results of using or not using LMWH for individual types of fracture, the 181 patients were categorized according to type of fracture and whether LMWH was used or not: 81 had a fracture in the intertrochanteric femur (of which 49 used LMWH and 32 did not) and 100 had a fracture in the femoral neck (Fig. 1).

Of the 181 patients, four had DVT (2.20%), all of whom were in the LMWH user group (3.44%). All DVT cases occurred in the calf vein and did not propagate to the proximal vein. No significant difference was found between the group that used LMWH and the group that did not use LMWH ($p=0.298$) (Table 2). In the subgroups analysis there was no significant differences (Table 3 and 4).

There were no cases in either group that showed melena, hematuria, nasal bleeding, or hematoma requiring re-operating. While three cases of thrombocytopenia (platelet $<100 \times 10^3 / \mu\text{L}$) occurred in the group that used LMWH and two cases in

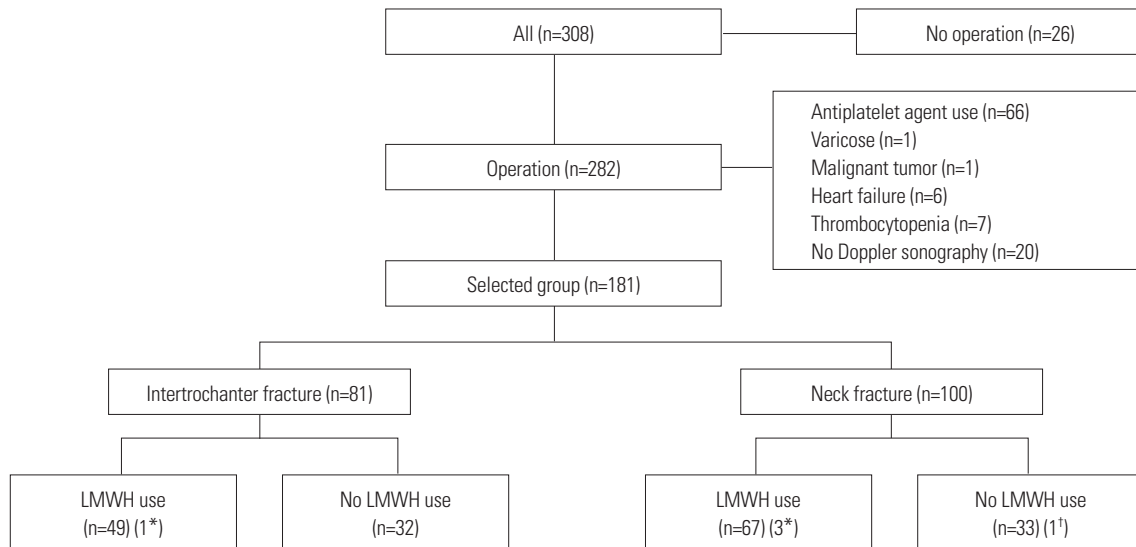


Fig. 1. Flowchart and proportion of patients with surgery type and LMWH use confirmed deep vein thrombosis. *Deep vein thrombosis, †Pulmonary thromboembolism. LMWH, low molecular weight heparin.

Table 1. Baseline Demographics and Clinical Characteristics of Population According to Use of Low Molecular Weighted Heparin

	LMWH	No LMWH	p value
Patient (No.)	116	65	
Age (yrs)	75.4±10.3	73.8±9.7	0.236
Male:female	38:78	22:43	0.702
Height (cm)	157.5±8.2	158.5±8.7	0.127
Weight (kg)	54.48±13.1	55.21±11.6	0.786
BMI (kg/m ²)	20.71±4.1	21.25±3.9	0.101
Time to operation (day)	4.23±3.1	4.34±2.8	
Type of fracture			0.37
Intertrochanter fracture (No.)	49	32	
Femur neck fracture (No.)	67	33	
Type of operation			0.266
Bipolar arthroplasty (No.)	65	28	
Cannulated screw fixation (No.)	2	5	
PFNA (No.)	43	30	
DHS (No.)	6	2	
Type of anesthesia			0.414
General (No.)	79	48	
Spinal (No.)	37	17	

BMI, body mass index; PFNA, proximal femur nail anti-rotation; DHS, dynamic hip screw; LMWH, low molecular weighted heparin; No., number.

Table 2. Patient Number of Pulmonary Embolism and Deep Vein Thrombosis in the All Fracture

	LMWH	No LMWH	p value
DVT	4	0	0.298
PE	0	1	1.000

DVT, deep vein thrombosis; PE, pulmonary embolism; LMWH, low molecular weighted heparin.

Table 3. Patient Number of Pulmonary Embolism and Deep Vein Thrombosis in the Femur Intertrochanteric Fracture

	Femur intertrochanteric fracture		p value
	LMWH	No LMWH	
DVT	1	0	1.000
PE	0	0	

DVT, deep vein thrombosis; PE, pulmonary embolism; LMWH, low molecular weighted heparin.

Table 4. Patient Number of Pulmonary Embolism and Deep Vein Thrombosis in the Femur Neck Fracture

	Femur neck fracture		p value
	LMWH	No LMWH	
DVT	3	0	0.549
PE	0	1	0.330

DVT, deep vein thrombosis; PE, pulmonary embolism; LMWH, low molecular weighted heparin.

the group that did not use LMWH, there was no statistically significant difference therein ($p=0.591$).

DISCUSSION

The prevalence rate of VTE after orthopedic surgery is known to be 40–84% for total knee replacement (TKR), 45–57% for total hip replacement (THR), and 40–84% for hip fracture. In the case of THR, the incidence is higher among black people than among Caucasians, and the incidence is lowest among Asians.^{7–10}

Our study results show that the incidence of VTE after HFS is 2.2%, which is similar to the 3.5% incidence rate reported by Ji, et al.,⁴ although this is a lower rate than those reported in studies conducted in Caucasians. The difference in results of THR had been reported to be affected by genetics, such as the activated protein C resistance known as factor V Leiden,¹¹ prothrombin G 20210A variation,¹² and shortage of anti-thrombin.¹³ Kim and Kim¹⁴ explained that DVT after THR in a Korean population showed a significantly lower prevalence rate than that in Caucasians, that no mutation was present in activated protein C or prothrombin G 20210A, and that anti-thrombin was within the normal level. The authors thought that the difference in these factors also played a role in the occurrence of VTE after hip fracture. The authors also thought that another reason why the incidence of VTE was low in their study was associated with the fact that most of the fractures were fall related osteoporotic fracture. Osteoporosis is correlated with a low body mass index rather than obesity, which are related risk factors of VTE. In addition, in our study, the body mass index of the patients was lower than the normal range (Table 1 and 2).^{15,16}

Type of surgery type may affect differences in the incidence of VTE after HFS. Schiff, et al.¹⁷ reported that existing risk fac-

tors of VTE, such as old age, sex, obesity, malignant tumor, heart failure or a recent myocardial infarction, increases the occurrence of VTE by two- to nine-fold. However, the effects of such factors have been reported to be minimal after orthopedic surgery. In particular, TKR and THR have been found to be important factors affecting prevalence rate. In our study, none of the 93 patients with femoral neck fracture had undergone THR, and only bipolar hemiarthroplasty was performed.

Non-movement is an important risk factor for DVT. Two days after operation, we removed the drainage, and continuous passive motion (CPM) devices were started. From 3 days after operation, we started a tilt-table standing practice. If the patients withstand the tilt-table standing, ambulation was started. In this study, recovery of ambulation took an average of 4.61 days. Rosendaal¹⁸ reported that, compared with patients without paralysis, those whose limbs are paralyzed had a nine-fold increased prevalence rate of DVT. They also reported that the time from which the patient is injured to the actual surgery after hip fracture has an effect and that, in cases where the surgery is delayed by more than 1 day, the incidence increases by 14.5%. In cases where it was delayed by 7 days or more, the rate increased by 33.3%.^{1,19} Collaboration with other departments is necessary to operate as soon as possible for the treatment of older patients with hip fractures. Hence, forming a team specialized in hip fracture can help reduce the duration from injury to surgery and may help prevent the occurrence of VTE.

In our study, we did not observe any melena, hematuria, nasal bleeding, and hematoma that required re-operation. We think that this may be because we used a low dosage of 2500 IU; however, we did not compare this with an administration of 5000 IU. Seven patients had thrombocytopenia, although no significant difference was found between the LMWH user and non-user groups.

The incidence of VTE across the different types of fracture was compared in the sub-group analysis. No significant difference was found between whether LMWH was used or not in the two groups. This may be because the overall prevalence rate of VTE is low, or we assume it may be because none of the 93 patients with femoral neck fracture had undergone THR, as only bipolar hemiarthroplasty had been done.²⁰

Proximal DVT that progresses into PE has significance. In studies on DVT with symptoms, proximal vein thrombosis has been reported to occur in 50–90% of patients who underwent THR and 40–50% of patients who underwent TKR.^{21,22} However, in our study all DVT cases occurred in the calf vein, accompanying no PE. This difference may be due to the above-mentioned ethnic differences, although it could also be due to a difference in the surgical method. In particular, for TKR, this can be explained by the use of a tourniquet and damage to the inner cellular lining of the arteries when the inserted object enters.³ While it is rare for a thrombus in the calf vein to develop into PE, when thrombus with symptoms is not treated,

it has been reported to progress to the proximal vein in 16–33% of the cases and develop into PE in 40–50% of the cases. Therefore, if thrombus occurs in the calf vein, continuous treatment is required.²³

One case of PE occurred in the LMWH non-user group in this study, although no significant difference in usage of LMWH was found. In the group with PE, DVT was not observed. In cases where only PE occurs without DVT, the mechanism has yet to be explained fully. This can be explained by cases where it occurs in the pulmonary artery, cases where the thrombus is completely separated from the distal artery, or cases where a false negative result might be obtained in the ultrasound test.²⁴

This study has a few limitations. First, while it was conducted prospectively, selection bias is possible owing to the instances of administering LMWH every 2 weeks. Second, considering that the incidences of DVT and PE in Asians are low, the study subjects were relatively few. Therefore, the results may not be representative of the entire Korean population. In power analysis, we found that a sample size of 181 cases provided 90% power ($\beta=0.1$; $\alpha=0.05$) to detect a significant difference in the incidence of DVT or PE between LMWH user group and non-LMWH user group using the McNemar test of equality of paired proportions (nQuery Advisor 4.0, Statistical Solutions, Cork, Ireland). Third, Doppler ultrasonography, which was used in this study is non-invasive and could be used repeatedly. However, the results differ depending on the size and location of the thrombus, the skill of the test conductor, and whether the patient was cooperative. In particular, for the femoral vein, the diagnostic rate is low. Fourth, the authors conducted the ultrasonographic test on the 10th day after discharge; however, VTE and PE have been reported to occur naturally up to 30 days after surgery. Therefore, this study is limited in that it only assessed the likelihood of DVT and PE in the early stages.²⁵

In conclusion, the administration of LMWH was not found to be effective in the prevention of VTE and PE in Korean patients who underwent HFS.

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