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Preventive effects of low molecular weight heparin on formation of deep vein thrombosis by reducing D dimer values in patients undergoing spinal surgery

X. YIN, P. LIU, B.-Y. LIU, Y.-Y. LIU, W.-L. FAN, J.-H. ZHAO

Department of Spinal Surgery, Institute of Surgery Research, Daping Hospital, Third Military Medical University, Chongqing, China

Abstract. – OBJECTIVE: Deep vein thrombosis (DVT) is one of the most common complications for patients undergoing spinal surgery. This study aims to investigate preventive effects of low-molecular-weight heparin (LMWH) on the formation of DVT.

PATIENTS AND METHODS: This study involved 37 patients who underwent spinal surgery between April 2016 and April 2017. Patients were divided into LMWH group and Control group. Clinical parameters, including operation time, intra-operative blood loss, incision length, post-operative visual analogue scale (VAS), exercise-time leaving bed and post-operative extubation time, were collected. Blood routine analysis, including platelet count (PLT), red blood cell count (RBC), white blood cell count (WBC) and hemoglobin (HGB) were also conducted. Coagulation parameters, including prothrombin time-international normalized ratio (PT-INR), fibrinogen (FIB), activated partial thromboplastin time (APTT), thrombin time (TT), prothrombin time 1 (PT-1) and D-dimer (DD), were evaluated. The drainage fluid was collected.

RESULTS: LMWH treatment significantly decreased operative time, blood loss and incision length compared to Control group at 1st, 3rd and 7th day post-operation (all $p<0.05$). LMWH treatment significantly increased WBC levels compared to Control group at 1st, 3rd and 7th day post-operation ($p<0.05$). LMWH treatment significantly decreased DD levels in the post-operative patients compared to Control group at 1st, 3rd and 7th day post-operation ($p<0.05$). However, LMWH treatment doesn't affect drainage amounts of patients. DD levels were positively correlated with WBC counts for the LMWH treated patients.

CONCLUSIONS: Low molecular weight heparin effectively prevents the formation of DVT by reducing DD values in patients undergoing spinal surgery.

Key Words:
Deep vein thrombosis, Low-molecular-weight heparin, D-dimer, Spinal surgery.

Introduction

The venous thromboembolism (VTE) is a kind of potentially lethal and a common disorder that mainly includes pulmonary embolism (PE) and the deep vein thrombosis (DVT)[1,2]. The VTE is considered to be correlated with the smoking, advanced age, major surgery, obesity, neurological deficit, hospitalization, malignancy, immobilization, and the oral contraceptive use[3,4]. The DVT is one of the most common complications for the spinal surgery in clinical, which could cause the fatal PE[5], and the DVT risk-factors commonly exist in the degenerative spine patients[6]. In the clinical spine surgery, there are many risk factors for the venous stasis, including lack of the muscle tone, long-period horizontal ventral decubitus, venous compression by the retractors and the post operative bed rest[7]. The low-molecular-weight heparin (LMWH) is considered to an effective regent for controlling DVT of the patients who inflicted from the spinal cord injury, selective surgery, according to the guidelines of National Institute of the Health and Care Excellence (NICE) and the American College of the Chest Physicians (ACCP)[8]. LMWH is considered to be the gold standard anticoagulant treatment posts the joint and limb surgery, which is characterized by the minimal effects on the hemostasis and doesn't increase bleeding-risk[9]. Meanwhile, there are also a few studies[3,10] which reported the controversial conclusions for the application and effects of LMWH in clinical.

Corresponding Author: Jian-Hua Zhao, MD; e-mail: yeenxiang@yeah.net

However, the LMWH is seldom applied to the spinal surgery in clinical, due to the opening of the spinal canal in spinal surgery always causes the hemorrhoea (the hemorrhoea also compresses the spinal cord)[11-13]. The previous study reported that the post-operative D-dimer (DD) is an effective biomarker for the occurrence of DVT, and the DD concentration higher than 500 μg/L is considered to be a risk factor of DVT post spinal surgery[14]. Meanwhile, the other coagulation factors[15], including prothrombin time-international normalized ratio (PT-INR), fibrinogen (FIB), activated partial thromboplastin time (APTT), thrombin time (TT), prothrombin time 1 (PT-1), were also examined to evaluate the DVT of spinal surgery patients. Therefore, the present prospective study selected the spinal degenerative diseases patients undergoing transforaminal lumbar interbody fusion (TLIF) operation, investigated the effects of LMWH on the occurrence of the DVT in the spinal disease patients.

Patients and Methods

Patients and Trial Grouping

The present clinical trial is a prospective trial that included 37 patients who underwent the spinal surgery between April 2016 and April 2017. The inclusive criteria were all the complete-records, including the patients' age, weight, sex, admission data, occupation, DVT, hospital stay, spinal epidural hematoma, surgical method, duration of operation, size of incision, blood loss, PT-INR, FIB, APTT, TT, PT-1, DD and the blood routine. The exclusive criteria were listed as the followings: 1- the percutaneous vertebroplasty and conservative therapy, since the patients were discharged soon from our hospital post the percutaneous vertebroplasty; 2- patients who suffered from the DVT prior to the operation; 3- patients who took the anti-coagulants, such as the clopidogrel, aspirin and warfarin one week prior to the hospital admission. All of the 37 patients were divided into two groups, including Low molecular heparin group (n=26) and Control group (n=11). The patients in Low molecular heparin group were administrated with the Low molecular heparin according to the previously published study[7]. The patients in Control group were administrated without any drugs.

This study was approved by the Ethics Committee of Daping Hospital, Third Military Medical University, Chongqing, China. All of the informed consents were obtained from the patients and all of the patients have approved this study.

Clinical Parameters Collection

During the processes of the operation, the clinical parameters, including operation time (min), intraoperative blood loss (ml), incision length (cm), post-operative visual analogue scale (VAS) scores, exercise time leaving bed (day) and post-operative extubation time (day), were collected according to diagnostic method and criteria in the previous studies[16,17].

Blood Sample Collection and Blood Routine Evaluation

The blood samples were selected for the blood routine analysis, including platelet count (PLT), red blood cell count (RBC), white blood cell count (WBC) and hemoglobin (HGB). The baseline values prior to the surgery and the values at 1st, 3rd and 7th day post-operation for hematology were collected. All of the above hematological parameters were measured by utilizing the Cell-Dyn Sapphire[18,19] hematology analyzer (Abbott Diagnostics, Santa Clara, CA, USA).

Coagulation Function Test

The commercial reagents were employed to measure the PT-INR (Symex Co., Kobe, Japan), FIB (Diagon Ltd, Budapest, Hungary), APTT (Sysmex, Kobe, Japan), TT (Symex Co., Kobe, Japan) and PT-1 (Sysmex Co., Kobe, Japan) by using the ACL-TOP700 automated blood coagulation analyzer (Beckman Coulter Inc., Brea, CA, USA) according to the manufacturer's instruction. The human-specific D-dimer ELISA kit (American Diagnostica Inc., Stamford, CT, USA) was employed to evaluate the DD values according to the instructions of manufacturer.

Drainage Fluid Collection

From the first day post operation, the abdominal cavity drainage fluid was harvested at 1st day, 3rd day and 7th day post operation, until the liquid drainage tube was pulled-up. Then, the drainage fluid amounts were measured as the conventional method described in the previous study[20].

Statistical Analysis

All of the data were expressed as the means ± SD and analyzed by using the SPSS 19.0 software (SPSS, Inc., Armonk, NY, USA). The x^2-test was used for comparing the differences between groups for categorical variables. The Student's t

test was used to analyze the differences between the data normally distributed, and Mann-Whitney test was used for non-normally distributed continuous variables. *p*-value less then 0.05 was considered as the significant.

Results

Basic Characteristics for Patients Included

Among all of the 37 spinal surgery patients, a total of 26 patients were admitted to the LMWH and 11 patients were untreated with LMWH. The 37 patients included 17 males and 20 females, aged from 51 to 80 years old (median of 60.69 for patients admitted to LMWH *vs.* median of 63.82 for patients without LMWH treatment, $p>0.05$). Therefore, there were no significant differences for gender, age, pre-operative VAS scores (7.92 *vs.* 8), pre-operative coagulation parameters (PT-INR, FIB, APTT, TT, PT-1 and DD) and pre-operative blood routine (PLT, WBC, RBC and HGB), between Low molecular weight heparin group and Control group (Table I, $p>0.05$).

LMWH Treatment Decreases Operative Time, Blood Loss and Incision Length

In order to confirm the effects of LMWH treatment on the clinical outcomes of patients, the operation time, intra-operative blood loss, incision length, post-operative VAS scores, exercise time leaving bed and post-operative extubation time have been compared between two groups. The results showed that operation time was significantly decreased in Low molecular heparin group (100.38 days) compared to Control group (119.09 days) (Table II, $p=0.046$). The intraoperative blood loss was significantly decreased in Low molecular heparin group (107.69 ml) compared to Control group (172.73 ml) (Table II, $p=0.024$). Meanwhile, the incision length in Low molecular heparin group (8.15 cm) was also significantly shorter compared to Control group (11 cm) (Table II, $p=0.037$). However, there were no differences for the post-operative VAS score (1.54 *vs.* 1.36), exercise time leaving bed (3.15 days *vs.* 3.3 days), post-operative extubation (4 days *vs.* 4.4 days), between Low molecular heparin group and Control group (Table II).

LMWH Treatment Increases WBC Levels in the Post-operative Patients

In this study, the blood routine parameters post-operation, including PLT, WBC, RBC and HGB, were also measured and compared between two groups. The results indicated that the WBC levels were significantly increased in Low molecular heparin group compared to Control group at 1st day, 3rd day and 7th day post-operation, respectively (Table III, $p=0.043$, 0.024 and 0.046, respectively). However, the LMWH treatment can't affect the levels of PLT, RBC and HGB of patients post operation (Table III, $p>0.05$).

LMWH Treatment Decreases DD levels in the Post-Operative Patients

In order to test the effects of LMWH on the DVT of patients, the DVT specific coagulation biomarkers including, PT-INR, FIB, APTT, TT,

Table I. Basic characteristics of the patients in both group.

Characteristics	Low molecular heparin group (n=26)	Control group (n=11)	*p*-value
Gender (male/female)	12/14	5/6	0.064
Age (years)	60.69 (46-78)	63.82 (51.00-80.00)	0.072
Pre-operative VAS score	7.92 (6-10)	8 (7-9)	0.084
Pre-operative coagulation function			
PT-INR	0.96 (0.83-1.15)	0.995 (0.92-1.09)	0.059
FIB (g/L)	3.33 (1.75-5.80)	2.842 (2.16-4.34)	0.093
APTT (s)	32.02 (26.50-38.00)	31.55 (29.10-36.00)	0.078
TT (s)	13.96 (11.40-16.20)	15.04 (12.40-17.20)	0.068
PT-1 (s)	10.82 (8.00-12.50)	11.34 (10.50-12.40)	0.057
DD (μg/L)	168.45 (21.00-710.24)	147.36 (21.00-379.54)	0.069
Pre-operative blood routine			
PLT (109/L)	190.27 (104.00-282.00)	171.50 (81.00-264.00)	0.054
WBC (109/L)	5.97 (3.21011.73)	5.19 (2.32-7.00)	0.057
RBC (1012/L)	4.48 (3.50-6.20)	4.23 (3.68-4.69)	0.084
HGB (g/L)	136.04 (115.00-166.00)	130.50 (119.00-142.00)	0.089

Table II. The clinical outcomes of the patients post-operation.

Characteristics	Low molecular heparin group (n=26)	Control group (n=11)	*p*-value
Operation time (min)	100.38 (70-150)	119.09 (90-150)	0.046
Intraoperative blood loss (ml)	107.69 (50-300)	172.73 (50-500)	0.024
Incision length (cm)	8.15 (8-17)	11 (7-15)	0.037
Post-operative VAS score	1.54 (1-3)	1.36 (1-2)	0.18
Exercise time leaving bed (day)	3.15 (2-7)	3.3 (3-4)	0.37
Post-operative extubation time (day)	4 (3-6)	4.4 (2-6)	0.26

PT-1 and DD, were examined. The results showed that the LMWH treatment significantly decreased the levels of DD at 1st, 3rd and 7th day post-operation, compared to the Control group (Table IV, p=0.011, 0.004 and 0.003, respectively). However, there were no significant differences for the PT-INR, FIB, APTT, TT and PT-1 between the Low molecular heparin group and Control group at 1st, 3rd and 7th day post-operation (Table IV, p>0.05).

LMWH Treatment Doesn't Affect Drainage Amounts of Patients

We also examined the drainage amounts at 1st, 3rd and 7th day for both of Low molecular heparin group and Control group. The results showed that LMWH treatment has not affected the drainage amounts compared to Control group at 1st, 3rd and 7th day post operation (Table V, all p>0.05).

DD Levels Positively Correlate with WBC Counts in LMWH Treating Patients

The previous study reported that both of DD and WBC could reflect the inflammatory response degree, therefore, we investigated the correlation between DD levels and WBC counts. The results illustrated that the DD levels were positively correlated with the WBC counts for the LMWH treated patients at 1st day (Figure 1A), 3rd day (Figure 1B) and 7th day (Figure 1C), respectively (all p<0.05).

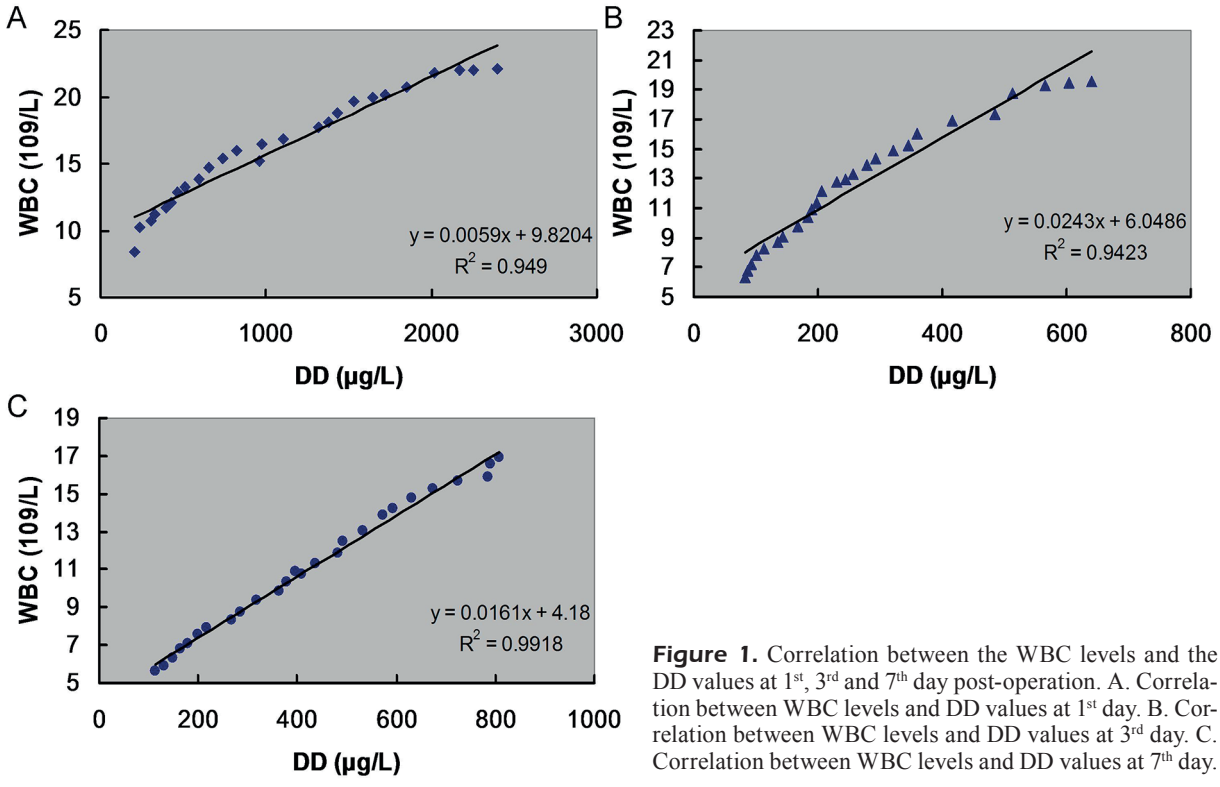

Figure 1. Correlation between the WBC levels and the DD values at 1st, 3rd and 7th day post-operation. A. Correlation between WBC levels and DD values at 1st day. B. Correlation between WBC levels and DD values at 3rd day. C. Correlation between WBC levels and DD values at 7th day.

Table III. The post-operative blood routine values for the patients.

	1st day post-operation			3rd day post-operation			7th day post-operation		
Post-operative blood routine	**Low molecular heparin group**	**Control group**	***p*-value**	**Low molecular heparin group**	**Control group**	***p*-value**	**Low molecular heparin group**	**Control group**	***p*-value**
PLT (10^9/L)	177.77 (109.00-270.00)	151.40 (96.00-204.00)	0.055	178.76 (100.00-264.00)	152.50 (95.00-198.00)	0.069	214.08 (139.00-327.00)	185.20 (114.00-274.00)	0.053
WBC (10^9/L)	12.17 (8.35-22.07)	10.08 (5.85-12.62)	0.043	11.03 (6.31-19.57)	8.50 (5.47-10.97)	0.024	10.18 (5.59-16.93)	9.64 (5.30-12.98)	0.046
RBC (10^{12}/L)	3.94 (3.10-5.35)	3.69 (3.24-4.22)	0.31	3.57 (2.79-4.74)	3.28 (2.47-3.93)	0.46	3.76 (3.11-4.89)	3.52 (2.55-4.10)	0.48
HGB (g/L)	119.69 (93.00-145.00)	112.80 (97.00-130.00)	0.74	108.68 (87.00-133.00)	100.90 (83.00-123.00)	0.89	113.85 (92.00-134.00)	107.60 (95.00-125.00)	0.39

Table IV. The post-operative coagulation functions of patients.

	1st day post-operation			3rd day post-operation			7th day post-operation		
Post-operative blood routine	**Low molecular heparin group**	**Control group**	***p*-value**	**Low molecular heparin group**	**Control group**	***p*-value**	**Low molecular heparin group**	**Control group**	***p*-value**
PT-INR	1.09 (0.91-1.27)	1.10 (1.01-1.25)	0.79	0.96 (0.89-1.16)	1.04 (0.92-1.20)	0.08	0.98 (0.88-1.16)	1.054 (0.93-1.30)	0.49
FIB (g/L)	3.69 (2.09-5.63)	3.07 (1.91-4.56)	0.37	4.02 (2.87-5.55)	3.11 (1.64-4.22)	0.054	3.35 (2.24-5.35)	2.61 (1.90-4.29)	0.42
APTT (s)	32.33 (25.80-48.00)	30.39 (25.10-36.30)	0.41	28.22 (21.20-33.40)	26.29 (19.90-30.90)	0.056	28.50 (21.70-35.00)	26.55 (22.70-30.40)	0.48
TT (s)	14.26 (11.70-23.00)	13.74 (12.60-16.10)	0.63	14.34 (11.80-16.70)	15.03 (13.20-17.00)	0.071	14.87 (11.20-19.20)	15.60 (14.06-17.00)	0.62
PT-1 (s)	12.41 (10.40-14.50)	12.57 (11.50-14.10)	0.72	10.96 (9.40-13.20)	11.84 (10.50-13.70)	0.067	11.13 (10.00-13.30)	12.03 (10.60-14.90)	0.48
DD (μg/L)	955.79 (206.53-2397)	1589.51 (333.00-7721)	0.011	290.75 (82.15-640.95)	1209.80 (234.25-3911.88)	0.004	334.74 (113.00-809.00)	1321.00 (153.00-4419)	0.003

Table V. The drainage at 1st, 3rd and 7th day post-operation.

Drainage	1st day post-operation			3rd day post-operation			7th day post-operation		
	Low molecular heparin group	Control group	*p*-value	Low molecular heparin group	Control group	*p*-value	Low molecular heparin group	Control group	*p*-value
Drainage amounts (ml)	151.08 (50.00-550.00)	206.82	0.052 (20.00-545.00)	51.27 (5.00-125.00)	79.20 (60.00-120.00)	0.069	72.5 (25.00-1120.00)	70.00 (30.00-75.00)	0.134

Discussion

The DVT is kind of most common complication of the patients undergoing the spinal surgery, which could also cause the fatal PE finally[21,22]. There are many factors affecting the occurrence of DVT post the spinal surgery, including age more than 60 years old, body mass index (BMI), thrombophilia, history of venous thrombosis, spinal cord damage, spinal trauma, *etc.*[9,23,24]. However, all of the above factors in the operation processes can't be avoided by employing the traditionally operative methods. Therefore, we employed the low-molecular-weight heparin to prevent the occurrence of the DVT in the patients who underwent the spinal surgery.

The low-molecular-weight heparin was applied as the first-line anticoagulation medicine and the gold standard for the patients undergoing the injury[25,26]. Meanwhile, the LMWH is also commonly applied to the bridging anticoagulation dependent on it's predictable pharmacokinetic characteristic[27]. The bridging anticoagulant therapy mainly prevents the thromboembolism and prevents the bleeding in the patients[28], which has been extensively applied in clinical.

In this study, some of the outcomes have been improved in the patients treated with low molecular weight heparin compared to the untreated patients. The results indicated that the operation time of patients in low molecular weight group was shorter significantly compared to the Control group (p=0.046). Meanwhile, the intra-operative blood loss was significantly reduced (p=0.024) and incision length was significantly shortened in Low molecular weight heparin group compared to Control group. According to the above findings, we found that the LMWH treatment could obviously decrease the blood loss, and therefore, shortened the operation time, which is consistent with the previous study[29]. Testroote et al[30] also reported that the low molecular weight heparin could effectively prevent the venous thromboembolism of the lower-leg immobilization patients. Guo et al[31] used the low molecular weight heparin and found that the LMWH significantly reduced the severity of the leg and the back pains in the patients post the lumbar decompressive surgery. VAS scores are the standard marker for the degree of the pain for the patients undergoing surgery; therefore, we evaluated the VAS scores in this study. This study illustrated that there were no significant differences for post-operative VAS score between Low molecular weight group and

Control group (p=0.18). This result suggests that the LMWH couldn't add the additional pains in the spinal surgery, lumbar surgery operation and the other surgical operations in clinical.

The previous study[32] reported that the WBC is an independent and indirect predictor for the inflammatory responses during a few diseases. Zhang et al[33] showed that the full blood count parameter acts as an aid for monitoring the asthma inflammatory factor. The WBC is routinely determined as a part of the workup for the patients with abdominal pain[34]. Therefore, we speculated that the LMWH may be associated with the inflammatory response in the patients and tested the post-operative blood routines, including PLT, WBC, RBC and HGB levels, in LMWH treated patients. The results indicated that the WBC levels were significantly increased in Low molecular weight group compared to Control group at 1st, 3rd and 7th day post the operation (p=0.043, 0.024 and 0.046, respectively). However, there were no significant differences for the PLT, WBC and HGB between Low molecular weight heparin group and Control group (p>0.05). The results suggest that the LMWH activated the anti-inflammatory response (production of WBC) in order to antagonize the inflammation post the surgical operation.

Till now, a few biomarkers labeling the activated hemostatic-system, such as the DD levels, hyper-fibrinogenemia and thrombocytosis, have been exhibited in a few cancers and the thrombotic diseases[35,36]. The present work investigated the significant differences between the Control health patients and patients treated with low molecular weight heparin with respect to the coagulation tests, including PT-INR, FIB, APTT, TT, PT-1 and DD. In this study, the DD levels were significantly reduced in patients treated with LMWH compared to the Control patients at 1st, 3rd and 7th day post-operation (p=0.011, 0.004 and 0.003, respectively), which may caused by the activation of the coagulation system. However, the other coagulation factors have not illustrated the significant changes comparing the two groups. DD as a biomarker for the coagulation and fibrinolytic activation, is a specific predictor for the DVT, which has been proved by several previous studies[37,38]. Our results suggest that the DD reduction may play an important role in the coagulation processes of LMWH treated patients, and LMWH prevents the formation of DVT in patients. Although the associated mechanism by which the coagulation is caused in patients is multifactorial, the tissue factor (TF) is the most identified marker in this process[39]. However, this study has not been evaluated the levels of TF in patients, which is a limitation of this study.

The previous studies[40,41] illustrated that both of the WBC levels and DD levels could reflect the inflammatory status. In this study, we investigated the correlation between the WBC levels and DD levels in the LMWH treated patients. The result indicated that the DD levels were significantly correlated with WBC counts for the LMWH treated patients. Therefore, we believed that the WBC may act as a promising biomarker for the occurrence of the DVT in clinical. However, the efficacy of the predictive role of WBC for DVT is also needed to be studied in the future study.

Moreover, the drainage amounts of the patients in two groups were also assessed in this study. The results showed that the application of LMWH has not influenced the drainage amounts at 1st, 3rd and 7th day post-operation comparing to Control group. Therefore, the results revealed that LMWH could inhibit the coagulation, but has not affect the post-operation drainage amounts.

Conclusions

The application of the low molecular weight heparin could shorten the operation time, reduce intraoperative blood loss and activate the anti-inflammatory function by triggering WBC production. What's most important is that the low molecular weight heparin effectively prevents the formation of DVT by reducing the values of DD in the patients. Moreover, low molecular weight heparin doesn't affect the drainage amounts and VAS post-operation.

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Conflict of Interest

The Authors declare that they have no conflict of interest.

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