https://doi.org/10.31925/farmacia.2022.6.12 **ORIGINAL ARTICLE**

EFFECT OF LOW MOLECULAR WEIGHT HEPARIN ON PREVENTION AND TREATMENT OF DEEP VENOUS THROMBOSIS IN ELDERLY PATIENTS WITH HIP FRACTURE AFTER OPERATION

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Manuscript received: August 2012

Abstract

The aim of this research was to investigate the preventive and therapeutic effects of low molecular weight heparin (LMWH) on postoperative deep venous thrombosis (DVT) in elderly patients with hip fracture, and to explore its mechanism of action and safety. Fifty-four elderly patients with hip fractures admitted to the hospital were randomly divided into a treatment group and a control group (27 cases for each group). The treatment group was subcutaneously injected with LMWH while the control group did not receive LMWH. The visual analogue scale (VAS) score of the control group was significantly increased compared with the treatment group at 4 and 7 days after the operation. Haemoglobin level (HGB) and platelet (PLT) count in the control group were significantly increased compared with the treatment group at 7 days after the operation. The D-dimer level in the control group was significantly increased compared with the treatment group on days 4 and 7 after the operation. The postoperative drainage volume in the control group was significantly increased compared with the treatment group. The incidence of postoperative deep venous thrombosis (DVT) in the control group (62.96%) was significantly increased compared with the treatment group (14.81%). The results showed that the use of LMWH in elderly patients with hip fracture after the operation could significantly reduce the pain of the affected limb, reduce the plasma D-dimer content, inhibit PLT proliferation, promote HGB recovery, and reduce postoperative drainage volume, with high safety.

Rezumat

Scopul acestei cercetări a fost evaluarea efectelor preventive și curative ale heparinei cu greutate moleculară mică (HBPM) asupra trombozei venoase profunde (TVP) postoperatorie la pacienții vârstnici cu fractură de șold și de a explora mecanismul său de acțiune și siguranță. Cincizeci și patru de pacienți vârstnici cu fracturi de șold internați în spital au fost împărțiți aleatoriu într-un grup de tratament și un grup de control (27 de cazuri pentru fiecare grup). Grupului de tratament i-a fost administrată subcutanat HBPM, în timp ce grupul de control nu a primit HBPM. Scorul scalei analog vizuală (VAS) al grupului de control a fost semnificativ crescut în comparație cu grupul de tratament la 4 și 7 zile după operație. Nivelul hemoglobinei (HGB) și numărul de trombocite (PLT) în grupul de control au fost semnificativ crescute în comparație cu grupul de tratament, la 7 zile după operație. Nivelul D-dimerului în grupul de control a fost semnificativ crescut în comparație cu grupul de tratament în zilele 4 și 7 după operație. Volumul de drenaj postoperator în grupul de control a fost semnificativ crescut în comparație cu grupul de tratament. Incidența trombozei venoase profunde (TVP) postoperatorie în grupul de control (62,96%) a fost semnificativ crescută comparativ cu grupul de tratament (14,81%). Rezultatele au arătat că utilizarea după operație a HBPM la pacienții vârstnici cu fractură de șold ar reduce semnificativ durerea membrului afectat și conținutul plasmatic de D-dimer, inhibă proliferarea PLT, favorizează creșterea HGB și reduce volumul de drenaj postoperator, cu valoare ridicată de siguranță.

Keywords: low molecular weight heparin (LMWH), elderly hip fracture, deep venous thrombosis (DVT), D-dimer

Introduction

Deep venous thrombosis (DVT) formation refers to abnormal coagulation of blood in the deep veins of the lower extremities, resulting in impaired blood return and symptoms such as limb swelling and pain [1-3]. In recent years, with the increase in the ageing population, the incidence of hip fractures in the elderly has shown an increasing trend, and data have shown that hip fractures are a high-risk factor for DVT formation [4-6]. Relevant studies have found that the incidence of DVT in patients after hip surgery is about 13% in China and worldwide [7-9]. Once DVT occurs, patients may experience thrombophlebitis, long-term swelling and pain of the lower limbs, and other symptoms, which directly affect the quality of life of patients. Therefore, it is very important to prevent and treat DVT in elderly patients with hip fractures.

Currently, with the in-depth exploration of DVT diseases by most physicians, various active preventive measures have gradually emerged. Among them, the main preventive measures include physical prophylaxis and pharmacological prophylaxis [10-13]. Physical prevention avoids the occurrence of venous thrombosis by promoting venous blood return, increasing blood

flow rate, decreasing blood stasis, and preventing the occurrence of venous thrombosis. The most common methods include elastic stockings and venous pump devices, which have the advantage of reducing the occurrence, the disadvantage is that it is inconvenient to use in trauma patients, and the final clinical efficacy has not been uniformly concluded [14-16]. Pharmacological prophylaxis is most used, including aspirin, heparin, and low molecular weight heparin (LMWH), of which LMWH is the most widely used in clinical practice [17-19]. Currently, LMWH as a change of fibrinolytic system and coagulation function of the body in clinical practice can prevent DVT, but with the increase of anticoagulant drug varieties, it also brings difficulties to clinical work. The most prominent problem is that although drug prevention can reduce the occurrence of DVT, it increases the risk of postoperative bleeding in patients.

The aim of this study was to evaluate the changes in visual analogue scale (VAS) score, thigh diameter difference, the incidence of DVT, and postoperative drainage volume in elderly patients with hip fractures after operation receiving or not LMWH and the underlying mechanism.

Materials and Methods

Study subjects

Fifty-four elderly patients with hip fractures admitted to the Beijing Luhe Hospital, Capital Medical University, Beijing, China from November 2020 to November 2021 were randomly divided into a treatment group (n = 27) and a control group (n = 27), with 25 males and 29 females and an average age of 74.84 ± 6.35 years. There was no significant difference in age, sex, cause of injury, and other general data between the two groups ($p > 0.05$), with comparability. This research was approved by the ethical committee of the Beijing Luhe Hospital, Capital Medical University, Beijing, China, while the patients and their families signed the informed consent form for participation in the study.

Inclusion criteria: (1) patients aged 65 years or older; (2) no fractures except hip, no open wounds; (3) negative DVT by colour Doppler; and (4) no previous history of thrombosis.

Exclusion criteria: (1) patients aged < 65 years; (2) patients with major organ complications (heart, liver, kidney); (3) patients with coagulation dysfunction; and (4) patients allergic to this experimental drug or its components.

Surgery and treatment methods

Patients in both the control and treatment groups were treated with conventional epidural anaesthesia, healthy lateral decubitus position, and posterolateral hip approach. Antibiotics were used to prevent infection before and after surgery. After surgery, the affected limb needed to be placed in abduction neutral position to avoid joint detachment and the analgesic pump was retained for 2 to 3 days. On the second day after surgery, active functional exercise of the joint muscles of the affected limb was performed in both groups to prevent the formation of DVT.

In the control group, routine active functional exercise of the joint muscles of the affected limb was performed without LMWH.

The treatment group was subcutaneously injected with 100 AxzIC·U/kg LMWH injection (Hebei Changshan Biochemical Pharmaceutical Co., Ltd., China, approval number: H20063909) 12 hours before surgery, 12 hours after surgery, and 24 hours after surgery, 100 AxzIC·U/kg LMWH on days 2 and 3, and 150 AxzIC·U/kg LMWH on day 4, which continued until day 7 after surgery.

Colour Doppler ultrasonography

DD70 colour ultrasonic diagnostic system (Foshan Ruijia Medical Technology Co., Ltd, China) was used to examine the occurrence of DVT. Criteria for judging DVT: the diameter of the vein is significantly dilated, and the lumen can't be completely closed; the lumen of the vein is anechoic or hypoechoic; there is a very small amount of blood flow signal in the venous thrombosis segment, or there is no blood flow signal at all; the thrombus in the lumen of the vein drift freely with limb extrusion; ultrasound shows no blood flow signal and it does not change with the change of respiration.

Clinical outcome measures

Pain changes: VAS score scale was used to assess the pain changes of patients [20]. Using a ruler with 10 scales labelled 0-10 on the corresponding scale, "0" means no pain and "10" means intense pain. VAS scores were recorded at 1, 4 and 7 days after surgery.

Swelling changes: The circumference of the affected limb at 15 cm from the upper edge of the patella of the healthy limb was measured at 1, 4 and 7 days after surgery in both groups by the same physician, and the thigh circumference difference was calculated.

Postoperative drainage volume: 24 h - 48 h after operation, the drainage tube was removed, read by the same experimenter, and the total drainage volume in the drainage bag was recorded.

Incidence of DVT: Colour Doppler ultrasound examination of lower limb venous vessels was performed by experienced physicians in the colour Doppler ultrasound room to examine the presence or absence of lower limb venous thrombosis. Specialist treatment was performed after diagnosis.

Plasma D-dimer content test: LMWH-anticoagulated plasma was collected and detection was carried out by colloidal gold immuno-penetration assay (kit purchased from Nycomed, Norway), and plasma D-dimer content was measured according to the kit instructions.

Fasting venous blood was collected from patients before and after surgery at 8 a.m. and tested by automatic coagulation function analyser (Type:

ACLTOP700; Werfen, Germany) and related reagents. It mainly included coagulation function (prothrombin time (PT), activated partial thrombin time (APTT), and fibrinogen (FIB)), and inflammatory indicators such as C-reactive protein (CRP) levels. Automatic blood cell analyser (Type: Unicel DXH 800; BECKMAN. COULTER, USA) and supporting reagents were used to detect blood routine (platelet and haemoglobin).

Statistical methods

All data were analysed by Excel and SPSS 21.0 statistical software (IBM, NY, USA). Measurement data were expressed as mean ± standard deviation, enumeration data were analyzed by chi-squared test (χ^2 test), and enumeration data were expressed as percentage (%). Differences were statistically significant at a $p < 0.05$.

Results and Discussion

General data

In the control group, there were 13 males and 14 females, with an average age of 75.39 ± 6.37 years, 19 femoral neck fractures, and 8 intertrochanteric fractures. There were 13 cases of artificial hemi-arthroplasty, 6 cases of artificial total hip arthroplasty and 8 cases of internal fixation. In the treatment group, there were 12 males and 15 females with a mean age of 73.93 ± 6.46 years, 18 femoral neck fractures, and 9 intertrochanteric fractures. There were 12 cases of artificial hemiarthroplasty, 8 cases of artificial total hip arthroplasty, and 7 cases of internal fixation.

There was no significant difference in gender, age, fracture type, and surgical methods between the two groups ($p > 0.05$) (Table I).

Table I

Initial general data of the patients in the two groups

Parameter	Control group (n = 27)	Treatment group (n = 27)	p
Gender			0.372
Male	13 (48.14)	12 (44.44)	
Female	14 (51.85)	15 (55.55)	
Mean age (years)	75.39 ± 6.37	73.93 ± 6.46	0.251
Fracture type			0.534
Femoral neck fracture	19 (70.37)	18 (66.66)	
Intertrochanteric femur	8 (29.62)	9 (33.33)	
Surgical method			0.326
Hemiarthroplasty	13 (48.14)	12 (44.44)	
Total hip arthroplasty	6 (22.22)	8 (29.62)	
Internal fixation	8 (29.62)	7 (25.92)	

VAS score evaluation

There was no significant difference in VAS score between the two groups in day 1 after operation ($p > 0.05$). For inter-group comparison, the VAS scores on days 4 and 7 after operation in the control group were significantly increased compared with the values of the treatment group ($p < 0.05$). For intra-group comparison, VAS scores at 4 and 7 days after surgery were lower than those at 1 day after surgery, with significant differences ($p < 0.05$) (Figure 1).

Blood cell indicators evaluation

There was no significant difference in preoperative HGB between the two groups ($p > 0.05$). In both groups, HGB significantly decreased 1 day after surgery compared with the levels before surgery ($p < 0.05$). The HGB in the control group was significantly increased compared with the treatment group 7 days after the operation ($p < 0.05$) (Figure 2A).

There was no significant difference in preoperative PLT count between the two groups ($p > 0.05$). The PLT count on day 1 after the operation in the two groups was lower compared with the levels before the operation ($p < 0.05$). PLT in the control group was significantly increased compared with the treatment group on day 7 after the operation ($p < 0.05$) (Figure 2B).

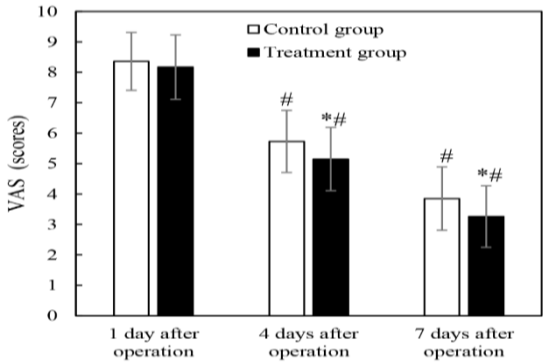

Figure 1.

Comparison of VAS scores between the two groups

* $p < 0.05$ compared with the control group;

# $p < 0.05$ compared with the first day of operation

Coagulation markers evaluation

There was no significant difference in preoperative PT, APTT and FIB levels between the two groups ($p > 0.05$). PT, APTT and FIB in the two groups showed different degrees of a significant decrease on day 1 after the operation compared with those before the operation ($p < 0.05$). PT, APTT and FIB on day 7 after the operation were significantly lower

in the control group compared with the levels in the treatment group ($p < 0.05$) (Figure 3).

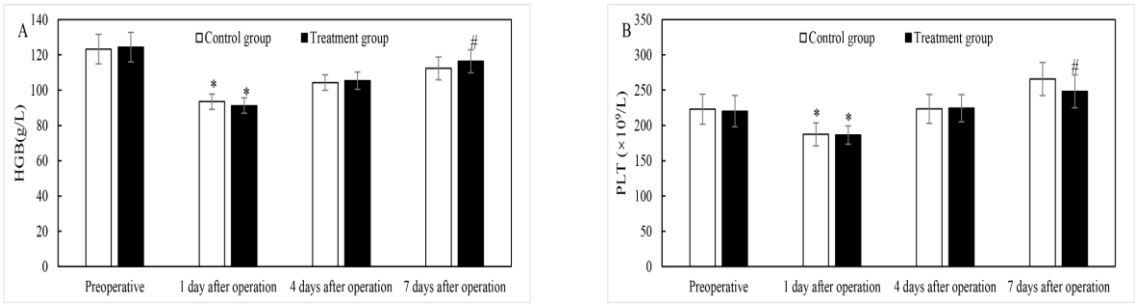

Figure 2.
Comparison of blood cell indicators:
A: Comparison of changes in HGB content; B: Comparison of changes in PLT count
*Compared with that before the operation, $p < 0.05$; # compared with control group, $p < 0.05$

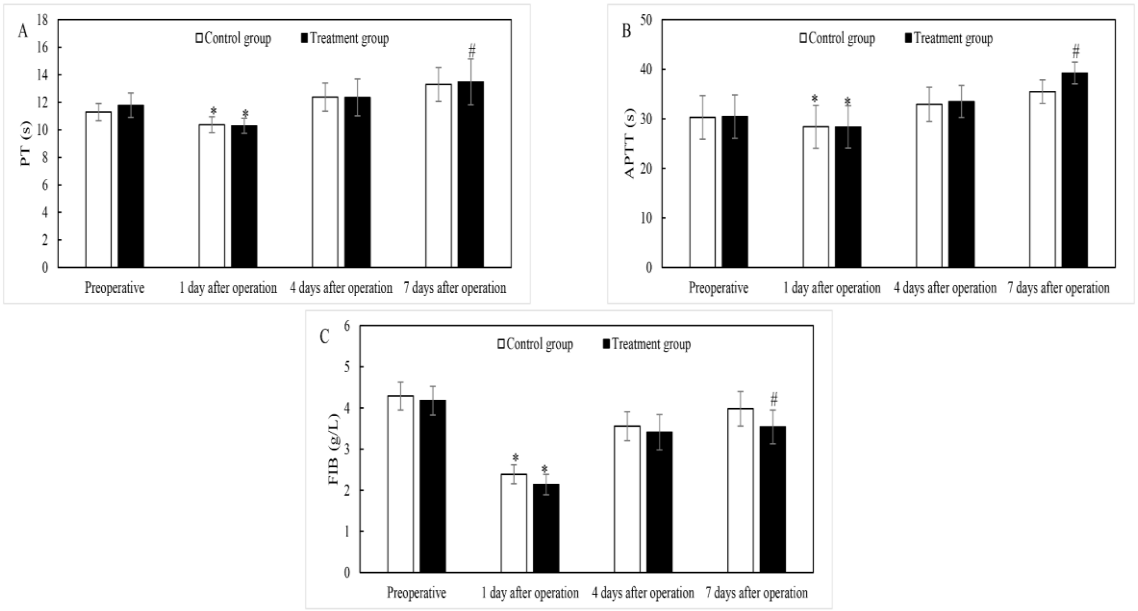

Figure 3.
Comparison of changes of coagulation indicators in each group. A: PT; B: APTT C: FIB
* Compared with the levels before operation $p < 0.05$; #compared with the control group, $p < 0.05$

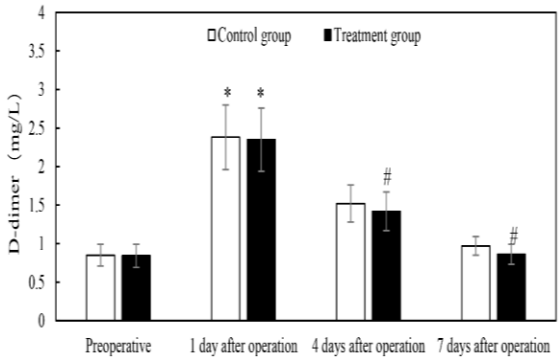

Figure 4.
Comparison of D-dimer level in plasma between the two groups
* compared with that before the operation, $p < 0.05$;
# compared with the control group, $p < 0.05$

D-dimer level in plasma evaluation

There was no significant difference in preoperative D-dimer level between the two groups ($p > 0.05$). The plasma D-dimer levels on day 1 after the operation in both groups were significantly increased compared with the levels before the operation ($p < 0.05$). The D-dimer level in the control group was significantly higher compared with the treatment group at 4 days and 7 days after operation ($p < 0.05$) (Figure 4).

CRP levels evaluation

There was no significant difference in CRP levels between the two groups 1 day after surgery ($p > 0.05$). The CRP level in the treatment group was significantly decreased compared with the control group on days 4 and 7 after the operation, (Figure 5).

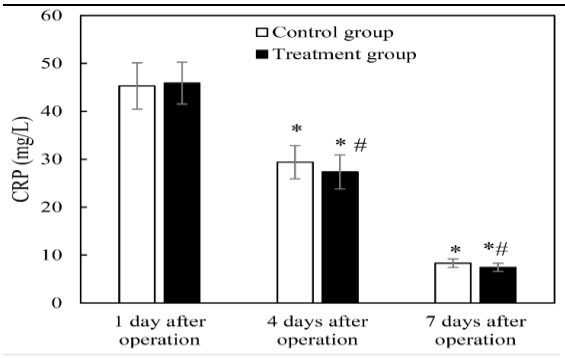

Figure 5.
Comparison of inflammatory marker CRP levels between the two groups
* Compared with the levels from day 1 after the operation, $p < 0.05$; # compared with the control group, $p < 0.05$

Thigh circumference difference evaluation

There was no significant statistical difference in the thigh circumference difference between the two groups before surgery ($p > 0.05$). The thigh circumference difference at 4 days after operation in the two groups was significantly increased compared with the levels before the operation ($p < 0.05$) The thigh circumference significantly increased in the treatment group compared with the control group 7 days after the operation ($p < 0.05$) (Figure 6).

Postoperative drainage volume evaluation

The postoperative drainage volume in the control group was significantly increased in the control group compared with the treatment group ($p < 0.05$) (Figure 7).

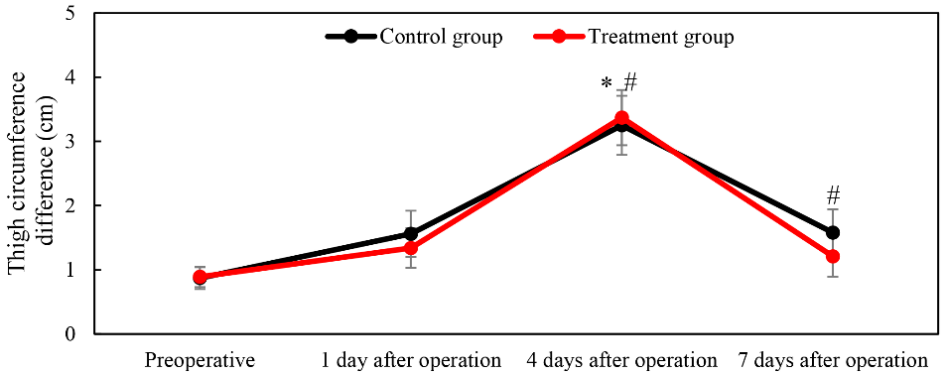

Figure 6.
Comparison of thigh circumference difference between the two groups
* Compared with the levels before the operation, $p < 0.05$; # compared with the control group, $p < 0.05$

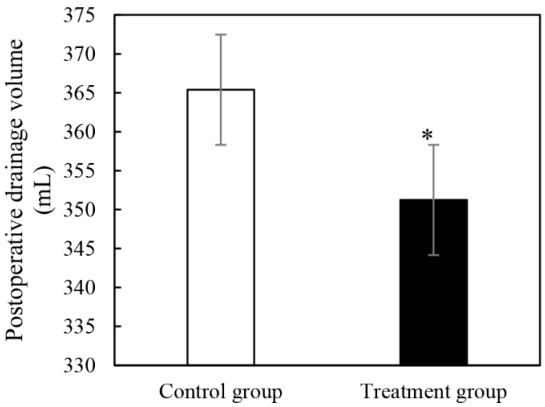

Figure 7.
Comparison of postoperative drainage volume between the two groups.
* Compared with the control group, $p < 0.05$

DVT incidence evaluation

In the control group, the incidence of postoperative DVT was 62.96%, including 5 cases of internal iliac vein embolization, 3 cases of femoral vein embolization, 7 cases of popliteal vein embolization and 2 cases of total embolization. The incidence of postoperative DVT in the treatment group was 14.81%, including popliteal vein embolization in 2 cases, femoral vein embolization in 1 case, internal iliac vein embolization in 1 case, and no patients with total embolization. It is observed a significant increase in DVT incidence in the control group compared with the treatment group ($p < 0.05$) (Table II).

Table II
Incidence of DVT [n (%)] in the two groups

Group	Femoral vein embolization	Internal iliac vein embolization	Popliteal vein embolization	Total embolization	Incidence of DVT
Control group (n = 27)	3	5	7	2	17 (62.96)
Treatment group (n = 27)	1	1	2	0	4 (14.81)
p					0.034

With the increase of age, due to osteoporosis and mobility difficulties, hip fracture is more frequent in the elderly, increasing the number of hip replacement operations. Postoperative DVT prevention and treatment directly affect the quality of postoperative rehabilitation. Currently, the main clinical prevention methods for DVT are anticoagulant drugs and early functional exercise [21-23]. LMWH is one of the most used anticoagulant drugs in clinical practice, which not only stimulates the release of plasminogen activator from vascular endothelium, but also accelerates fibrinolysis to reduce the agglutination of red blood cells as well as PLT in the blood [24]. Subcutaneous injection of LMWH after admission in the treatment group significantly reduced the incidence of DVT.

Blood index determination is an indirect observation method to evaluate human body function, which can be used for the clinical diagnosis of DVT. If the levels of FIB and fibrin-D fragments in human plasma increase, the risk of blood clots increases also. FIB is a coagulation factor that can bind to leukocytes and directly participate in the inflammatory response, while the occurrence of an inflammatory response can directly aggravate endothelial cell injury and promote the formation of DVT, therefore, FIB can be used as an inflammatory response marker [25-27]. The results showed that FIB in the control group was increased compared with the treatment group 7 days after the operation which was consistent with the results of Dong *et al*. [28]. When the body is stimulated by endogenous/exogenous stimuli, the body activates the prothrombin activator, activates prothrombin into thrombin, fibrinogen is converted into fibrin by the action of thrombin, and the formed fibrin network hemadsorption factor gradually forms clots.

D-dimer is a specific degradation product produced by plasmin hydrolysis of fibrin monomer activator after cross-linking. D-dimer content can reflect the lytic function of fibrin. The results showed that the content of D-dimer in the control group was significantly increased compared with the treatment group 4 days after the operation and 7 days after the operation, being consistent with the findings of Liu *et al*. [29]. When there is activated thrombosis and fibrinolysis in human blood vessels, D-dimer content increases. LMWH can activate plasminogen, plasminogen hydrolysis of fibrin can promote thrombolysis determining a strong antithrombotic effect, which can reduce bleeding. In addition, LMWH can promote blood flow, regulate blood viscosity, and improve the anti-thrombotic function of the body's vascular wall. Compared with conventional drug therapy, LMWH has a lower risk and does not require continuous monitoring [30].

Colour Doppler ultrasound can accurately diagnose the formation of DVT. Through non-invasive imaging of venous vessels and their surrounding tissues, dynamic blood circulation of venous vascular tissues can be observed to determine the location and severity of DVT. According to relevant data, the accuracy of colour Doppler ultrasound in the diagnosis of DVT is more than 75% [31]. The incidence of postoperative DVT was 62.96% in the control group and 14.81% in the observation group. This is sufficient to show that anticoagulant therapy with LMWH in elderly patients with hip fractures can effectively reduce the incidence of DVT and reduce haemorrhagic complications.

Conclusions

The results showed that the use of LMWH in elderly patients with hip fracture after the operation could significantly reduce the pain of the affected limb, reduce the plasma D-dimer level, inhibit PLT proliferation, promote the recovery of HGB, and reduce the postoperative drainage volume, with high safety. The shortcomings in this study are related to the case selection, all cases come from the same trauma orthopaedics department, along with the low sample size which may lead to a certain degree of deviation between the experimental results and the actual situation. In addition, only the occurrence of DVT within 7 days after surgery was assessed, and the long-term efficacy of postoperative medication was not assessed. Later studies should focus on long-term follow-up and explore the potential of LMWH to prevent DVT at a deeper level.

Conflict of interest

The authors declare no conflict of interest.

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