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Original Article

Efficacy and safety of low molecular weight heparin treatment, intermittent pneumatic compression therapy passive ankle exercise and nursing care in preventing deep venous thrombosis of the lower extremity following varicose vein surgery

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Abstract: Objective: This study was designed to investigate the differences of three modalities, low molecular weight heparin (LMWH) prophylaxis, intermittent pneumatic compression (IPC) therapy and passive ankle exercise, and nursing care in preventing deep venous thrombosis (DVT) in the lower extremity. Methods: A total of 352 patients undergoing varicose vein surgery and secondary care from January 2011 to December 2013 were selected for this study. The patients were randomly divided into control (n = 92), LMWH (n = 85), IPC (n = 87) and passive ankle exercise (n = 88) groups. The effect of the three different treatments and nursing care on prevention of DVT in the lower extremity was studied according to the clinical criteria (symptoms and signs), blood flow velocities, internal vessel diameters and coagulation index by Color Doppler ultrasonography, and activated partial thromboplastin time. A follow-up was performed for all patients and varicose recurrence rate and incidence of saphenous nerve injury were recorded. Results: Compared with the control group, the patients in the LMWH, IPC and passive ankle exercise groups showed reduced DVT incidence, and the passive ankle exercise group showed the least DVT incidence. There were significant differences in terms of blood flow velocities, internal vessel diameters, coagulation index, circumferences of the thigh and calf, and swelling indexes before and after operation in the LMWH, IPC and passive ankle exercise groups; but there was no significant difference among the three groups. The total efficacies (significant effective + effective + improved) of these three methods were 97.58%, 97.70% and 98.86%, respectively, and there was no significant difference. Conclusion: LMWH, IPC and passive ankle exercise all showed a certain effect on the prevention of DVT in the lower extremity. And the efficacy of passive ankle exercise was the strongest.

Keywords: Deep venous thrombosis, lower extremity, low molecular weight heparin, intermittent pneumatic compression, passive ankle exercise, varicose vein surgery

Introduction

Deep venous thrombosis (DVT), a common disease of the lower extremity, can cause permanent venous valve damage and 36% to 40% of DVT patients are found to develop pulmonary embolism (PE), which is associated with a mortality as high as 25% [1]. In addition, DVT may cause post-thrombotic syndrome (PTS) [2], which is likely the result of venous valve damage, venous hypertension and long-term venous obstruction, and has been reported in 20% to 100% of DVT patients [3]. Therefore, the efficacy of any DVT treatment shall be judged upon its ability to achieve following major clinical outcomes: (i) prevention of PE and future progression of DVT, (ii) relief of early symptoms, and (iii) prevention of PTS [4].

Currently, the therapies for DVT include both operative and non-operative methods. In terms of operative methods, endovascular interventions started in the early 1990s and were more efficient in reducing clot burden and thus giving a better life quality to DVT patients [5]. Catheter-directed thrombolysis (CDT), one of the most commonly used operative methods, relies on the infusion through a catheter located within the thrombosed vein to deliver a high local dose of thrombolytic agent, thereby breaking down the clot while minimizing systemic exposure to the thrombolytic agent [6].

When surgical treatment is not feasible or when the patients choose the conservative therapies, the anticoagulation therapy using heparin followed by oral anticoagulation agents is currently the most often used treatment for preventing PE and the relapse of DVT, although such treatment cannot prevent the onset of PTS, which can show up long after the DVT treatment is finished [2, 7]. Therefore, other non-operative methods have been developed, including passive ankle exercise [8], low molecular weight heparin treatment (LMWH) [9] and intermittent pneumatic compression (IPC) therapy [10] to prevent DVT. LMWH prophylaxis, a DVT treatment using a low molecular weight heparin related drug, is found to provide a similar efficacy as that of in-hospital therapies using the unfractionated heparin while at the same time demonstrating a potential advantage of allowing patients with moderate DVT to be treated at home [9]. During IPC, repeated expanding and retraction of an air bladder is applied to regulate the systemic blood pressure and to prevent the formation of thrombosis [11]. In addition, sequential foot and calf IPC as well as impulse foot IPC have been widely used in a clinical setting, and the influence of IPC on venous hemodynamics has been reported [12]. During passive ankle exercise, the gastrocnemius muscle is regularly contracted to speed up the flow of blood and it is found such movement of foot and ankle could decrease the incidence of DVT in the neuroscience intensive care patient population [13]. Although all of the above methods have shown a certain effect in the prevention of DVT, few studies have compared their efficacies. In this study, the efficacies of an LMWH treatment, an IPC therapy and an ankle exercise were compared and the cause of their differences was investigated.

Materials and methods

Ethical statement

The present study was performed in accordance with the guidelines established by Medicine Ethics Review Committee at The Second Affiliated Hospital of Harbin Medical University, and all patients have signed the forms of consent.

Study subjects

A total of 352 patients undergoing varicose vein surgery and nursing care in The Second Affiliated Hospital of Harbin Medical University from January 2011 to December 2013 were selected for this study. All patients showed varicose veins in the lower limbs [14]. Among the 352 patients, there were 173 males accounting for 49.1% and 179 females accounting for 50.9%. The age was 41 to 70 years old (55.13 ± 4.94 years old); the body weight was 42 to 103 kg (71.32 ± 11.28 kg); their body mass index (BMI) was 20.30~28.10 kg/m^2, average 24.10 ± 1.36 kg/m^2. The inclusion criteria were: varicose degree was in grade 3 according to Venous Clinical Severity Score [15]; no history of varicose vein stripping in the lower limbs; preoperative venography presented flow deep vinous and no iliac vein compression syndrome; with normal coagulation function; and no serious complications (such as heart failure, diabetes, arterial diseases and nervous system diseases). The exclusion criteria were: preoperative examination showed abnormal liver functions; a history of thrombocytopenia after using LMWH or allergic to LMWH; recent history of suppurative infection in the knees; distant unhealed infection, fracture or serious loss of function in knee extensor; secondary gravitropic deformity caused by myasthenia; poor general health condition that prevented the surgery. The patients were randomly divided into control group (92 cases), LMWH group (85 cases), IPC group (87 cases), and passive ankle exercise group (88 cases). No significant difference was found in the gender, age, body weight and BMI in the four groups, indicating comparativeness.

Treatments

The patients in the control group received no anticoagulant postoperatively, but received usual care. During the administration of LMWH prophylaxis [16], the patients underwent a high saphenous vein ligation + a segmental stripping surgery + an endovenous laser closure surgery under an epidural anesthesia. From day 1 after the surgery, the patients received subcutaneous LMWH injection (Fraxiparine, National medicine permission number: H200-63910) once a day for 4 continuous days, and the dosage was 4100 U/day by medical staff. The LMWH injection was stopped on the condition of bleeding at non-surgical sites, and that platelet count reduced to lower than 100 × 10^9/L, or abnormal liver functions were observed. For the patients treated with the IPC therapy [17], the drainage tube was removed from the incision on day 2 after the surgery and the treatment started using an air compressor (Daesung Industry Co., Ltd., Seoul, Korea). A pair of sleeves was put on to both legs of the patient by medical staff, and the mode-b pressurizing mode was chosen. The pressure was set to 26.6 kPa, and the treatment time was 20 min. The treatment was conducted once in the morning and once at night, and was continued for 2 weeks. For patients undergoing passive ankle exercises [18], the exercises were started immediately after the surgery. During the exercise, the gastrocnemius was held by the medical staff and the instep underwent plantar flexion and extension with the support from the left hand. The motion of exercise was dorsiflexion-inversion-plantar flexion-eversion. The range of dorsiflexion was 20°, the range of plantar flexion was 40°, and the range of both inversion and eversion was 30°. The movement frequency was 30 times/min, with each duration of the exercise lasting 8 minutes. The exercise was done once every 30 minutes and 20 times were done every day. The ankle exercises were carried out from day 1 to day 7 after the surgery. On each day, 7 exercises were arranged in the morning, 7 exercises were arranged in the afternoon and 6 exercises were arranged in the evening.

Criteria evaluation

After the surgery, the symptoms and signs of DVT in each of the three groups were monitored daily for swelling, numbness, pain, and skin color and body temperature. At 3 to 5 days after the surgery, conventional ultrasonography was performed for deep venous blood vessels in both lower limbs. The circumference of the lower limbs was measured daily after surgery.

Color Doppler ultrasonography was performed to measure the blood flow of the lower limbs in each of the three groups before the surgery and the next morning after the surgery. During the measurement, the patients relaxed and straightened their legs in order to measure the venous blood flow velocity and internal vascular diameters.

Activated partial thromboplastin time (APTT) was determined. The measurement was performed at 37°C, using kaolin to activate platelet factor XII and substituting platelet factor III with cephalin (partial thromboplastin). The time required for plasma coagulation was observed in the presence of Ca^{2+} and was determined as APTT.

At 7 days after the treatment, the efficacy was evaluated. Significant effect: signs and symptoms of varicose veins in the lower extremity completely disappeared, the thrombosis entirely dissolved, iliac and femoral veins showed no reflux as confirmed by ultrasonography, signs of limb swelling disappeared or almost disappeared, the difference in the circumference of lower extremity was < 1 cm; effective: symptoms and signs disappeared, most of thrombosis was dissolved, iliac and femoral vein recanalization was largely achieved as confirmed by ultrasonography, the difference in the circumference of lower extremity was < 1 cm; improved: symptoms and signs basically disappeared, edema improved during standing, some of thrombosis was dissolved, iliac and femoral vein recanalization was partially achieved as confirmed by ultrasonography, establishment of collateral circulation was significant, the difference in the circumference of lower extremity was still > 1 cm but the difference was significantly reduced compared to before the treatment; no effect: the difference in the circumference of lower extremity was not improved or even deteriorated after the treatment. The measurement of limb circumference was done in the following way: the patient was lying in a supine position and the limb circumference was measured with a soft tape. The circumference at 15 cm above the upper edge of the patella was used as the circumference of the thigh, and the circumference at 15 cm below the lower edge of the patella was used as the circumference of the calf. The difference of circumference = the circumference of the affected limb-the circumference of the normal limb.

Follow-up

All the 352 patients received a 4~12 months (average 9 months) follow-up through outpa-

Table 1. Comparison of clinical characteristics among the control, LMWH, IPC and passive ankle exercise groups

Clinical characteristics	Control (n = 92)	LMWH (n = 85)	IPC (n = 87)	Passive ankle exercise (n = 88)	*P*
Age (year)	55.16 ± 5.09	54.92 ± 4.60	55.71 ± 5.48	54.73 ± 4.55	0.588
Sex					
Male (cases)	43	41	47	42	0.767
Female (cases)	49	44	40	46	
Body weight (kg)	71.80 ± 11.39	70.10 ± 11.10	69.80 ± 10.70	73.50 ± 11.70	0.110
BMI (kg/m^2)	23.80 ± 1.30	24.20 ± 1.40	24.30 ± 1.20	24.10 ± 1.50	0.078
Course of disease (year)	9.03 ± 1.98	8.83 ± 1.89	8.63 ± 1.72	8.74 ± 1.84	0.526
Affected limbs					
Double lower limbs	32	27	28	29	0.999
Left lower limb	28	29	30	31	
Right lower limb	32	29	29	28	

Notes: LMWH, low molecular weight heparin; IPC, intermittent pneumatic compression; BMI, body mass index.

Table 2. Thrombosis in the control, LMWH, IPC and passive ankle exercise groups

Thrombosis	Control (n = 92)	LMWH (n = 85)	IPC (n = 87)	Passive ankle exercise (n = 88)	χ^2
Deep venous thrombosis	46 (50.00%)	29 (34.12%)*	26 (29.89%)*	15 (17.05%)$^{*,\#}$	22.60
Intramuscular thrombosis	41 (44.57%)	22 (25.88%)*	25 (28.74%)*	13 (14.77%)$^{*,\#}$	19.99
No thrombosis	5 (5.43%)	34 (40.00%)*	36 (41.38%)*	60 (68.18%)$^{*,\#}$	75.72

Notes: LMWH, low molecular weight heparin; IPC, intermittent pneumatic compression; $^*P < 0.05$ compared with the control group; $^\#P < 0.05$ compared with the LMWH or IPC group.

tient visits, telephone or online WeChat, once every month. The follow-up rate was 100%. Varicose recurrence rate and incidence of saphenous nerve injury were recorded.

Statistical analysis

The SPSS 19.0 statistical software (SPSS Inc., Chicago, IL, USA) was used. All measurement data were presented as mean ± standard deviation, and the comparison among groups was done using the single factor analysis of variance. The enumeration data were presented by percentage or rate, and the comparison was done using chi-square test. A P value < 0.05 was considered statistically significant.

Results

Clinical characteristics in the control, LMWH, IPC and passive ankle exercise groups

The clinical characteristics of the patients in the four groups were shown in **Table 1**. There was no significant difference in the four groups in terms of gender, age, body weight, BMI, course of disease or infected limbs (all P > 0.05).

Thrombosis in the control, LMWH, IPC and passive ankle exercise groups

After treatments by different preventive therapies, as can be seen from the postoperative observation, compared with the control group, the patients in the LMWH, IPC and passive ankle exercise groups showed significantly reduced incidence of DVT and intramuscular thrombosis, and increased number of patients with no thrombosis (all P < 0.05). The patients receiving all three methods showed certain effects in the prevention of DVT. The LMWH and IPC groups showed not significant differences in the incidence of DVT and intramuscular thrombosis, as well as no thrombosis rate (all P > 0.05). Compared with the patients in the LMWH and IPC groups, the patients in the passive ankle exercise group showed significantly decreased incidence of DVT and increased patients did not suffer from any thrombosis (all

Table 3. Preoperative and postoperative blood flow velocity, internal vessel diameter and coagulation index in the control, LMWH, IPC and passive ankle exercise groups

Item	Control (n = 92)	LMWH (n = 85)	IPC (n = 87)	Passive ankle exercise (n = 88)
Blood flow velocity (cm/s)				
Preoperative	23.87 ± 10.37	23.98 ± 10.32	23.95 ± 10.29	23.86 ± 10.42
Postoperative	32.58 ± 11.21*	28.65 ± 10.92$^{*,\#}$	28.34 ± 10.26$^{*,\#}$	28.73 ± 10.21$^{*,\#}$
Internal vessel diameter (mm)				
Preoperative	5.56 ± 0.61	5.54 ± 0.58	5.53 ± 0.56	5.49 ± 0.60
Postoperative	5.04 ± 0.48*	5.31 ± 0.52$^{*,\#}$	5.29 ± 0.62$^{*,\#}$	5.24 ± 0.55$^{*,\#}$
Coagulation index				
Preoperative	3.28 ± 1.26	3.36 ± 1.31	3.38 ± 1.26	3.17 ± 1.52
Postoperative	1.92 ± 0.86*	2.24 ± 0.88$^{*,\#}$	2.43 ± 1.05$^{*,\#}$	2.37 ± 0.13$^{*,\#}$

Notes: $^{*}P < 0.05$ compared with before preoperative values; $^{\#}P < 0.05$ compared with the control group; LMWH, low molecular weight heparin; IPC, intermittent pneumatic compression.

Table 4. Lower extremity circumferences and swelling index among the control, LMWH, IPC and passive ankle exercise groups before and after the operation

Item	Control (n = 92)	LMWH (n = 85)	IPC (n = 87)	Passive ankle exercise (n = 88)
Difference in thigh circumferences				
Preoperative	46.54 ± 4.14	47.23 ± 4.21	45.55 ± 4.32	43.87 ± 4.53
Postoperative	44.23 ± 3.86*	41.16 ± 3.97$^{*,\#}$	41.10 ± 3.84$^{*,\#}$	41.42 ± 3.89$^{*,\#}$
Difference	2.31 ± 5.41	6.07 ± 6.28	4.45 ± 6.07	2.45 ± 6.12
Difference in calf circumferences				
Preoperative	30.33 ± 2.51	30.57 ± 2.56	28.87 ± 2.15	26.96 ± 2.03
Postoperative	29.16 ± 2.13*	25.70 ± 2.21$^{*,\#}$	25.99 ± 1.89$^{*,\#}$	25.61 ± 1.77$^{*,\#}$
Difference	1.17 ± 3.18	4.87 ± 3.31	2.88 ± 2.90	1.35 ± 2.72
Swelling index (%)				
Preoperative	5.87 ± 0.67	5.35 ± 0.62	5.58 ± 0.55	5.24 ± 0.66
Postoperative	4.34 ± 0.48*	4.17 ± 0.43$^{*,\#}$	4.19 ± 0.37$^{*,\#}$	4.11 ± 0.37$^{*,\#}$

Notes: $^{*}P < 0.05$ compared with before preoperative values; $^{\#}$P < 0.05 compared with the control group; LMWH, low molecular weight heparin; IPC, intermittent pneumatic compression.

$P > 0.05$), indicating that and the effect of ankle exercise was the strongest (**Table 2**).

Blood flow velocity, internal vessel diameter and coagulation index in the control, LMWH, IPC and passive ankle exercise groups

There was no significant difference in blood flow velocities and internal vessel diameters among the four groups of patients before the operation (all $P > 0.05$). After the operation, the blood flow velocities and internal vessel diameters in the LMWH, IPC and passive ankle exercise groups had significantly improvement as compared to those before the treatments, specifically the blood flow velocities increased and the internal vessel diameters and coagulation index significantly decreased (all $P < 0.05$). However, there was no significant difference among the LMWH, IPC and passive ankle exercise groups in terms of blood flow velocity, blood vessel diameter and coagulation index (all $P > 0.05$) (**Table 3**).

Lower extremity circumference and swelling index among the control, LMWH, IPC and passive ankle exercise groups

The thigh and calf circumferences in the patients of all the four groups were measured daily after the surgery and there were significant differences before and after the treatment

Table 5. Efficacy in the control, LMWH, IPC and passive ankle exercise groups (%)

Efficacy	Control (n = 92)	LMWH (n = 85)	IPC (n = 87)	Passive ankle exercise (n = 88)
Significant effect	25 (27.17%)	34 (40.00%)#	38 (43.68%)#	37 (42.05%)#
Effective	21 (22.83%)	31 (36.40%)#	29 (33.33%)#	30 (34.09%)#
Improved	30 (32.61%)	18 (21.18%)#	18 (20.69%)#	20 (22.73%)#
No effect	16 (17.39%)	2 (2.35%)*	2 (2.30%)*	1 (1.14%)*

Notes: *$P < 0.05$ compared with the control group with no effect; #$P < 0.05$ compared with the control group with efficacy (significant effect + effective + improved); LMWH, low molecular weight heparin; IPC, intermittent pneumatic compression.

(all $P < 0.05$). The swelling index in the LMWH, IPC and passive ankle exercise groups after the surgery was significantly lower than that in the control group (all $P < 0.05$), but there was no significant difference among the LMWH, IPC and passive ankle exercise groups in terms of lower extremity circumference and swelling index (all $P > 0.05$) (**Table 4**).

Efficacy in the control, LMWH, IPC and passive ankle exercise groups

Compared with the control group, the rate of no effect in the LMWH, IPC and passive ankle exercise groups significantly decreased (all $P < 0.05$). The efficacies (significant effect + effective + improved) in the LMWH, IPC and passive ankle exercise groups were 97.58%, 97.70% and 98.86%, respectively, and there was no significant difference among the three groups, although they were significantly higher than that in the control group (**Table 5**).

Varicose recurrence rate and incidence of saphenous nerve injury in the control, LMWH, IPC and passive ankle exercise groups

There were 4, 3, 2 and 2 cases respectively in the control, LMWH, IPC and passive ankle exercise groups showing varicose recurrence, and 3, 2, 2 and 1 case respectively showing saphenous nerve injury. There were no significant differences in the four groups in terms of varicose recurrence rate and incidence of saphenous nerve injury (all $P > 0.05$) (**Table 6**).

Discussion

DVT can be caused by both genetic and acquired factors, wherein the most prominent risk factors are certain types of surgical operations as well as cancer, and moderate risk factors include hormone use and obesity [19]. In terms of clinical indications, blood hypercoagulability, slow venous blood flow and injury to vascular wall are the three main elements of venous thrombosis and promote the formation of blood clot by disrupting the equilibrium between the functions of coagulative and fibrinolytic systems [20]. Therefore, in this study, the efficacies of a LMWH treatment, an IPC therapy and a passive ankle exercise in preventing lower limb DVT were investigated through a comparative analysis.

From our results, it can be seen that the blood flow velocity, intravascular diameters and coagulation index in the patients of the LMWH, IPC and passive ankle exercise groups were significantly improved compared with those before operation, but there was no significant difference among the three groups. LMWH inhibits the activation of coagulation factor Xa [21]. The inactivation of the coagulation factor Xa in the presence of antithrombin (AT) is also associated with the inhibition of thrombin through the generation of a stable ternary complex with thrombin, AT and a polysaccharide compound that exerts a regulatory role on thrombin and coagulation activity [22]. IPC treatment can be performed by using inflatable sleeves that are placed around the legs and are secured by a fastener, while using a small bedside electric pump to provide pressure through a piece of flexible tubing to promote the blood circulation from the leg and to increase the venous flow, which results in increased venous blood flow through the deep veins of the lower extremity and reduced likelihood of thrombosis [23]. A previous study has shown that after the passive ankle exercises, the rate of blood flow significantly increased as compared to that during the resting, indicating that the passive ankle exercises may have a potential function to prevent DVT [8].

In our results, it was shown that the three treatments all showed certain effect on the prevention of DVT in the lower extremity. And accord-

Table 6. Varicose recurrence rate and incidence of saphenous nerve injury in the control, LMWH, IPC and passive ankle exercise groups

Item	Control (n = 92)	LMWH (n = 85)	IPC (n = 87)	Passive ankle exercise (n = 88)	χ^2	*P*
Varicose recurrence	4 (4.35%)	3 (3.53%)	2 (2.30%)	2 (2.27%)	0.908	0.824
Saphenous nerve injury	3 (3.26%)	2 (2.35%)	2 (2.30%)	1 (1.14%)	0.919	0.821

Notes: LMWH, low molecular weight heparin; IPC, intermittent pneumatic compression.

ing to the prognosis results, a relative small percent of patients suffering from varicose recurrence and saphenous nerve injury after operation, and there were no significant differences in the four groups in terms of varicose recurrence rate and incidence of saphenous nerve injury. It has been reported that when patients with active cancer and acute venous thromboembolism were treated with dalteparin, the risk of recurrent venous thromboembolism was significantly decreased [24]. On the other hand, a trend of reduced DVT risk was observed in patients treated with IPC as compared to that of the control group, although 2.2% of critically ill patients still developed deep veins and proximal veins thrombosis after IPC treatment [11]. Furthermore, the patients in the passive ankle exercise group showed decreased incidence of DVT and increased patients did not suffer from any thrombosis compared with the patients in the LMWH and IPC groups, indicating that the efficacy of passive ankle exercise was the best. This is expected since the movement of the ankle joint can promote the winding and stretching of the joint in different directions and change the pressure within joint. In addition, the ankle movement will undoubtedly speed up blood flow and reduce blood stasis, resulting in improved blood coagulation status and avoiding the formation of thrombus. Additionally, compared with the preoperative values, the thigh and calf circumferences and swelling index in the three experimental groups were significantly different, but there was no significant difference among the three groups themselves, indicating that the three treatments have a similar efficacy in terms of lower extremity circumferences and swelling index.

In summary, it can be seen from the results of this study that the passive ankle exercise can significantly improve the coagulation index, reduce the occurrence of venous thrombosis in the lower limbs, improve the patient's coagulation status, prevent the formation of DVT and is important to strengthen the circulation and metabolism in the entire blood system. Passive ankle exercise can be performed at home and is an effective, non-invasive, reliable and safe treatment with no risk of cross-infection, thus decreasing the financial burden to the patients and shall be widely used [25]. Clearly, the comparative analysis of the three treatments has some limitations. The patients selected for all three treatments were taken from a population receiving varicose vein operations and hence were prone to the onset of postoperative DVT. In addition, these patients may have some differences in terms of personal life styles and medical history that are not tracked.

Disclosure of conflict of interest

None.

Abbreviations

LMWH, low molecular weight heparin; IPC, intermittent pneumatic compression; DVT, deep venous thrombosis; PE, pulmonary embolism; PTS, post-thrombotic syndrome; CDT, catheter-directed thrombolysis; BMI, body mass index; APTT, activated partial thromboplastin time.

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