© Med Sci Monit, 2009; 15(11): CR588-593
PMID: 19865059

WWW.MEDSCIMONIT.COM
Clinical Research

Received: 2008.05.24
Accepted: 2008.11.21
Published: 2009.11.01

A comparison of different treatment managements in patients with acute deep vein thrombosis by the effects on enhancing venous outflow in the lower limb

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A Study Design
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Source of support: Departmental sources

Summary

Background: This study aimed at evaluating the benefits of the traditional management of acute deep vein thrombosis (DVT), subcutaneous (sc) administration of low-molecular-weight heparin (LMWH) one dose a day and bed rest, and LMWH with compression stocking and early ambulation compared with LMWH with pneumatic compression (PC) in patients with DVT.

Material/Methods: Forty-eight consecutive patients with DVT were separated evenly into four groups. Group A received intravenous unfractionated heparin, group B received sc injection of enoxaparin sodium and bed rest, group C received sc injection of enoxaparin sodium and thigh-length compression stockings, and group D received sc injection of enoxaparin sodium and PC for periods of up to 7 days.

Results: Comparing days 0 and 7, significant differences were determined in each group regarding differences in circumference of the two legs at the thigh and calf levels and the visual analogue scale (VAS) of pain, and in groups B, C, and D regarding the Lowenberg test for diseased and healthy legs ($p<0.001$). Between days 0 and 7, significant differences were found in the superficial femoral artery, superficial femoral vein, femoral vein, and the popliteal vein within groups A and D ($p<0.05$).

Conclusions: Traditional management, sc administration of low-molecular-weight heparin, and pneumatic compression of patients with DVT led to a faster reduction of leg swelling and pain and to increased volume flow through the deep veins of the legs.

key words: **deep vein thrombosis • pneumatic compression • venous outflow • color Doppler sonography**

Full-text PDF: http://www.medscimonit.com/fulltxt.php?ICID=878244

Word count: 2889
Tables: 3
Figures: –
References: 16

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Background

Deep vein thrombosis (DVT) is a common disorder, with an incidence rate of approximately 1 case per 1000 persons per year [1]. Although the risk factors and prophylaxis for DVT are well known, morbidity and mortality have been an important problem in DVT [2]. About 30% of the mortality occurs in patients with DVT due to pulmonary emboli [3]. Post-thrombotic syndrome (PTS), which is a chronic condition consisting of leg pain, edema, venous ectasia, skin induration, and ulceration, occurs in approximately 20 to 50% of patients with DVT and usually becomes established within the first two years after the acute thrombotic episode [1].

DTV is conventionally treated with an intravenous infusion of unfractionated heparin for at least 5 days followed by a course of oral anticoagulants. Hospital admission and bed rest for the duration of intravenous infusions have been recommended with the goal of avoiding leg movement to protect patients from pulmonary embolism (PE) [4]. This traditional management of DVT has changed considerably since the approval of subcutaneous administration of low-molecular-weight heparins (LMWHs) for the treatment of DVT. The use of LMWH is widespread due to the incidence of low hemorrhage, subcutaneous administration once or twice a day, and no need for close monitoring of anti-coagulation [2]. In the past, patients with active DVT were placed on bed rest for periods of up to 7 days due to the fear of PE [5]. Since subcutaneous administration of LMWHs for the treatment of DVT has widened, these patients can be treated without hospitalization. By investigating DVT patients with repeated lung scanning, we were able to demonstrate that there is no increased danger of PE if mobile patients are treated with LMWH and kept walking with compression bandages, regardless of the size or location of the thrombi [1].

In the present study, in addition to the traditional management of DVT, subcutaneous administration of LMWHs at one dose a day, graduated compression stockings, early ambulation, and pneumatic compression (PC) of patients with DVT were administrated to compare the effects on enhancing venous outflow in the lower limb using color Doppler sonography (CDS).

Material and Methods

This study was a randomized unblinded controlled trial in which four groups of adjuvant treatment modalities in patients with acute symptomatic DVT were compared. An institutional review board approved this study by Firat University, Medical Faculty, Elazig, Turkey. We considered 48 consecutive patients older than 18 years with DVT (thrombosis of deep veins of the legs) that was documented with compression ultrasound scan and clinical study. Patients received detailed information concerning the nature of this trial, including the risks associated with the seven-day period. Exclusion criteria were more than 24 hours of previous treatment with heparin or warfarin; need for thrombolytic therapy or thrombectomy; known hemorrhagic risk, including active hemorrhage, active intestinal ulcerative disease, known angiodysplasia, or eye, spinal, or central nervous system surgery within the previous month; severe hepatic insufficiency; allergy to heparin or protamine; history of coagulopathy-, heparin-, or warfarin-associated skin necrosis; known pregnancy or lactation; and the presence of pulmonary embolism. If we did not measure the peak systolic velocity using CDS for a patient in any venous segment, they were excluded from this study; the number of patients who were excluded from the study was seven.

Clinical scores were calculated for the following seven symptoms: pain during walking, painful foot sole, painful calf on palpation, subfascial edema, prefascial edema, increased skin temperature, and redness/cyanosis. The severity score comprised four stages (absent, mild, marked, and severe) so that a maximal score of 28 could be reached. Prefascial edema was defined as a palpable indentation of the skin after firm pressure was applied for more than 10 seconds by the thumb. An increase in the consistency of the calf palpated in a relaxed lying position of the patient was defined as subfascial edema. The circumference of the leg was measured at the mid-thigh and mid-calf levels.

DVT was diagnosed by the Wells score and ultrasound. During the seven days of the study the patients underwent several examinations. These included daily measurements of pain level, which was assessed by the Visual Analogue Scale (VAS) and the bilateral Lowenberg test. Pain was assessed daily at the same time with the two methods. The spontaneous sensation of pain was assessed by the patient on the VAS and, in a more objective way, with the modified Lowenberg test, in which a cuff was applied on each calf without removing stockings. Pressure was applied and the value at which the patient perceived pain in each calf was recorded. The measurements were repeated within a few minutes and the mean value was calculated. The difference between the thrombosed and the healthy leg was calculated and used for analysis.

Color Doppler sonography was performed using a Toshiba Aplio SSA-770A color Doppler ultrasound scanner (Tokyo, Japan). Examinations of the common femoral artery (FA) and vein (FV), superficial FA and FV, and popliteal artery (PA) and vein (PV) were performed using a 6- to 13-MHz broadband linear array transducer. The examinations were performed with the patient lying in a supine position with the head slightly elevated (about 20–30 degrees). The PV was evaluated with the patient's knee flexed in external rotation in a supine position or in a prone position. Venous segments were examined continuously in B-mode; compressibility of these veins was assessed at 2- to 3-cm intervals in the axial plane. CDS with pulsed Doppler and augmentation maneuver was used to document venous flow. CDS was performed mainly in a longitudinal plane. If venous segments were fully compressible and blood flow was seen within the veins on CDS evaluation, the examination was categorized as normal. If venous segments were non-compressible or blood flow was not present within the venous lumen on CDS evaluation, the examination was categorized as a complete thrombus. If venous segments were partially compressible or an intraluminal filling defect was seen in the vein on CDS, the examination was categorized as partial thrombus. Peak systolic velocities of examined veins and arteries were measured before and after seven days of therapy.

Groups

Group A: Intravenous infusion of unfractionated heparin and bed rest: Group A patients received intravenous unfraction-

Table 1. Baseline characteristics of patients according to treatment group.

Variable	Group A (n=12)	Group B (n=12)	Group C (n=12)	Group D (n=12)	*p* value
Age (y)	53.08±18.01	44.67±23.78	51.08±19.39	47.83±14.66	*ns*
Weight (kg)	73.08±13.21	74.35±12.80	71.50±11.40	77.55±15.60	*ns*
Female/male	10/2	8/4	7/5	4/8	*ns*
Wells score	4.08±0.90	4.17±1.26	4.00±0.95	3.75±1.05	*ns*
Clinical score	18.17±2.72	16.42±3.39	17.17±3.35	15.00±2.21	*ns*

ns – not significant ($p>0.05$).

ated heparin, with a bolus starting dose of 80 IU/kg bodyweight. Then the patients received an intravenous infusion of 18 IU/kg/hour unfractionated heparin for 7 days. On the first day the coagulation process was measured every 6 hours by the activated partial thromboplastin time (aPTT) and later once a day by aPTT and activated coagulation time (ACT). Platelet count was measured on days 3–5. The aPTT and ACT values were kept between 1.5-2.5 times the control value. The patients also received (as of day 3) oral anticoagulants (warfarin 5 mg/day) with doses adjusted to reach international normalized ratio values of between 2 and 3. The patients were advised to stay in bed. At the end of day 7 the patients were discharged with compression stockings. Warfarin was administrated for at least three months.

Group B: Low-molecular-weight heparin and bed rest: Group B patients received subcutaneous injection of enoxaparin sodium (clexane forte 12,000 U, 150 mg/kg/day) for up to 7 days. They also received (as of day 3) oral anticoagulants (warfarin 5 mg/day) with doses adjusted to reach international normalized ratio values of between 2 and 3. The patients were advised to stay in bed but were allowed to get up to use the toilet. At the end of day 7 the patients were discharged with compression stockings. Warfarin was administrated for at least three months.

Group C: Low-molecular-weight heparin and compression stocking: Group C patients received subcutaneous injection of enoxaparin sodium (clexane forte 12,000 U, 150 mg/kg/day) for up to 7 days. They received ready-made thigh-length compression stockings which were adapted to the individual leg size. They were worn both day and night. The patients were encouraged to walk as much as possible on the ward and on the hospital grounds. They also received every day (as of day 3) oral anticoagulants (warfarin 5 mg/day) with doses adjusted to reach international normalized ratio values of between 2 and 3. At the end of day 7 the patients were discharged with compression stockings. Warfarin was administrated for at least three months.

Group D: Low-molecular-weight heparin and pneumatic compression: Group D patients received subcutaneous injection of enoxaparin sodium (clexane forte 12,000 U, 150 mg/kg/day) for up to 7 days. They also received (as of day 3) oral anticoagulants (warfarin 5 mg/day) with doses adjusted to reach international normalized ratio values of between 2 and 3. The patients were immobile after they were admitted to the hospital. Intermittent pneumatic compression (SCD Response Compression System, Kendall, England) was established and this was applied to the ankle (2 seconds, 45 mmHg), calf (5.5 seconds 40 mmHg), and thigh (11 seconds 30 mmHg). At the end of day 7 the patients were discharged with compression stockings. Warfarin was administrated for at least three months.

Statistical analysis

Descriptives are quoted as the mean ±*SD* or numbers. One-way analysis of variance, the independent samples *t* test, paired samples *t* test, and the chi-squared test were used for the statistical analyses. For multiple tests, Tukey's method was used. A *p* value ≤0.05 was regarded as statistically significant.

RESULTS

Of the 48 eligible patients admitted because of proximal DVT between January 2007 and January 2008, all provided written consent to participate in this study. The baseline characteristics of the treatment groups are given in Table 1. The baseline characteristics were similar and there were no significant differences in age, weight, or gender among the groups. The clinical score was highest in Group A. The clinical score and Wells score for DVT diagnosis were not significantly different in the groups ($p>0.05$, Table 1).

Table 2 shows the differences in circumference of the two legs at the thigh and calf levels, VAS, and the Lowenberg test on days 0 and 7. On day 0 the differences in circumference for the calf were significantly higher in the bed-rest group than in the pneumatic compression group. There were no differences among the four groups at the calf level and thigh level on days 0 and 7 ($p>0.05$). Regarding VAS, statistically significant differences were found in groups B and D on day 0, whereas there was no significant difference on day 7. No statistically significant differences for the Lowenberg tests for diseased and healthy legs on days 0 and 7 among the groups were achieved. When comparing days 0 and 7, significant differences were determined in each group for the differences in circumference of the two legs at the thigh and calf levels and in VAS ($p<0.001$), and in groups B, C, and D for the Lowenberg test for the diseased and healthy legs ($p<0.001$). No significant differences were found in group A for the Lowenberg test for the diseased leg between days 0 and 7 ($p>0.05$).

Table 3 presents the comparisons of FA, SFA, PA, FV, SFV, and PV between days 0 and 7. Based on the results, statistical significant differences were found between days 0 and 7 in SFA,

Table 2. Differences in circumference of the two legs at the thigh and calf levels (cm), Visual Analogue Scale, and Lowenberg test on days 0 and 7 (mean ±*SD*).

Variable	Group A (n=12)	Group B (n=12)	Group C (n=12)	Group D (n=12)	Statistical difference
Difference in calf circumferences, day 0	5.83±2.43	5.13±2.48	4.58±2.24	3.29±1.28	A-D, *p*=0.03
Difference in calf circumferences, day 7	1.58±1.83	1.08±1.83	1.08±1.07	0.67±0.98	*ns*
Difference in thigh circumferences, day 0	6.75±3.48	6.83±4.91	4.96±3.22	3.58±3.05	*ns*
Difference in thigh circumferences, day 7	3.08±2.93	2.5±3.34	1.42±1.73	0.75±1.48	*ns*
Visual Analogue Scale, day 0	8.83±1.52	9.33±0.98	8.79±1.19	7.79±1.19	B-D, *p*=0.02
Visual Analogue Scale, day 7	2.50±0.79	2.08±0.78	2.08±1.24	1.67±0.65	*ns*
Lowenberg test, diseased leg, day 0	108.33±37.13	124.17±28.43	110.00±25.58	124.58±26.75	*ns*
Lowenberg test, diseased leg, day 7	242.92±38.73	163.75±33.65	142.08±17.64	157.92±30.26	*ns*
Lowenberg test, healthy leg, day 0	167.50±29.86	186.25±35.96	168.75±21.01	174.58±26.92	*ns*
Lowenberg test, healthy leg, day 7	261.25±36.37	190.42±18.64	173.75±21.22	179.58±26.15	*ns*
Statistical difference					
Difference in calf circumferences, day 0 vs. day 7	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	
Difference in thigh circumferences, day 0 vs. day 7	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	
Visual Analogue Scale, day 0 vs. day 7	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	
Lowenberg test, diseased leg, day 0 vs. day 7	*ns*	*p*<0.001	*p*<0.001	*p*<0.001	
Lowenberg test, healthy leg, day 0 vs. day 7	*ns*	*p*<0.001	*p*<0.001	*p*<0.001	

ns – not significant (*p*>0.05).

FV, SFV, and PV within groups A and D ($p<0.05$). There were no differences in FA and PA within groups A and D or in FA, SFA, PA, FV, SFV, and PV within groups B and C ($p>0.05$).

Discussion

Venous thromboembolism is usually treated with a minimum of five days of heparin therapy overlapping with warfarin, which is continued for at least three months. Unfractionated heparin, given by continuous intravenous infusion with ongoing dose adjustment in response to measurements of the activated partial thromboplastin time (aPTT), has been the standard approach to initial treatment [6]. The results of several controlled trials suggest that subcutaneous LMWH in selected, uncomplicated patients with DVT is as safe and effective as intravenous unfractionated heparin and that most patients can be treated as outpatients or discharged early [5]. Randomized trials and meta-analyses have also shown that subcutaneously administered LMWHs have antithrombotic efficacy equal to or greater than that of continuously infused unfractionated heparin in the initial treatment of deep vein thrombosis [7].

Another study demonstrated that compression stockings are able to dramatically reduce the frequency of post-thrombotic

Table 3. Comparisons of peak systolic velocities (cm/s) of FA, SFA, PA, FV, SFV, and PV on days 0 and 7.

Group	Variable	N	Mean	*SD*	*p*
Group A	FA, day 0	12	72.317	12.916	0.146
	FA, day 7	12	75.183	11.081	
	SFA, day 0	12	76.475	9.819	**0.034**
	SFA, day 7	12	80.830	9.197	
	PA, day 0	12	52.583	8.912	0.583
	PA, day 7	12	52.875	10.341	
	FV, day 0	12	6.817	8.466	**0.034**
	FV, day 7	12	8.042	7.645	
	SFV, day 0	12	5.740	5.292	**0.007**
	SFV, day 7	12	7.892	6.030	
	PV, day 0	12	4.058	2.413	**0.031**
	PV, day 7	12	6.492	6.756	
Group B	FA, day 0	12	64.240	12.990	0.937
	FA, day 7	12	64.400	14.255	
	SFA, day 0	12	64.710	9.072	0.388
	SFA, day 7	12	65.317	12.838	
	PA, day 0	12	44.742	4.603	0.170
	PA, day 7	12	47.183	8.234	
	FV, day 0	12	6.492	4.561	0.054
	FV, day 7	12	8.958	6.112	
	SFV, day 0	12	7.227	6.681	0.110
	SFV, day 7	12	9.950	7.552	
	PV, day 0	12	7.642	6.749	0.158
	PV, day 7	12	10.740	5.973	
Group C	FA, day 0	12	64.240	12.990	0.672
	FA, day 7	12	64.400	14.255	
	SFA, day 0	12	64.710	9.072	0.379
	SFA, day 7	12	65.317	12.838	
	PA, day 0	12	44.742	4.603	0.321
	PA, day 7	12	47.183	8.234	
	FV, day 0	12	6.492	4.561	0.149
	FV, day 7	12	8.958	6.112	
	SFV, day 0	11	7.227	6.681	0.126
	SFV, day 7	11	9.950	7.552	
	PV, day 0	12	7.642	6.749	0.263
	PV, day 7	12	10.740	5.973	
Group D	FA, day 0	12	76.742	14.957	0.347
	FA, day 7	12	73.883	13.729	
	SFA, day 0	12	76.117	11.154	**0.042**
	SFA, day 7	12	80.430	12.182	
	PA, day 0	12	47.867	8.092	0.610
	PA, day 7	12	47.908	8.980	
	FV, day 0	12	8.908	5.046	**0.038**
	FV, day 7	12	11.133	6.869	
	SFV, day 0	12	8.325	8.866	**0.034**
	SFV, day 7	12	8.925	5.881	
	PV, day 0	12	6.050	8.637	**0.025**
	PV, day 7	12	8.342	6.898	

PA – Popliteal artery; FA – femoral artery; SFA – superficial femoral artery; FV – Femoral vein; SFV – superficial femoral vein; PV – popliteal vein.

syndrome some years after proximal DVT, but compression therapy was started only several days after hospital admission [8]. Compression stockings also lead to a significantly faster and more extensive pain reduction than bed rest. Pain results from an increase in compartmental pressure resulting from the congestion of muscle veins by thrombi and trapped blood. It is generally thought that pain is reduced if the thrombosed leg is immobilized. The spontaneous decrease in compartmental pressure is slow. That external leg compression in conjunction with walking leads to a palpable reduction of subfascial consistency is probably due to a lowering of compartmental pressure and thus to a decrease in pain. Indirect support for this assumption is that the decreased subfascial lymph transport in patients with DVT is enhanced by firm external compression [9].

During exercise of patients with DVT, muscle contraction increases the pressure outside the veins and propels blood back to the heart (calf muscle pump), reducing the hydrostatic pressure gradient required for edema formation [10]. However, due to a decrease in arteriolar resistance, muscle blood flow increases above control conditions between contractions (active hyperemia) [5]. Normally, the venous system easily accommodates this increased flow, but venous obstruction or reflux, which can occur after DVT, might raise venous pressure to the extent that outflow cannot match inflow. The resultant increased volume within the vascular bed could raise capillary pressure, promote fluid transudation from the capillaries into the interstitial space, and impair leg muscle perfusion [11,12]. These phenomena could promote exercise-induced leg swelling and, potentially, worsening of venous symptoms due to both edema and muscle fatigue [1].

Application of pneumatic compression (PC) to the ankle, calf, and thigh is a well-proven prophylactic method of treating deep vein thrombosis. Flow augmentation on application of PC is achieved by an increase in the arteriovenous pressure gradient and, possibly, by the release of endothelium-dependent vasodilating factors [13,14] and by transient suspension of the venoarteriolar reflex, a local sympathetic reflex which, on elevation of the lower-limb venous pressure, causes peripheral arterial resistance to increase and flow to decrease [15].

The beneficial effect of PC systems on DVT prophylaxis is due to their prevention of venous stasis and enhancement of fibrinolytic activity. On delivery of an impulse, the pulsatility of venous flow [3], the peak and mean velocities, increase, causing lower-extremity veins to empty and flush away the activated clotting factors, the accumulation of which would promote thrombus formation [3]. PC produces significant increases in venous flow volume and flow velocity and acceleration of flow compared with baseline flow without a pump. This is true whether the limbs are elevated, horizontal, or dependent. Segmental flow changes with the position of the patient and the placement of the compression garment on the extremity. Calf compression provides maximal increases in volume flow and flow velocity through the deep veins of the calf and thigh [2].

There is only one report in the literature about PC treatment for acute DVT, which is usually recommended for DVT prophylaxis [2]. Adding PC to low-dose catheter-directed thrombolysis is effective in increasing leg venous flow. This method likely inhibits the progression of thrombus and maintains the patency of deep veins as effectively as walking mobilization reduces the progression of thrombus in acute DVT treated with anticoagulation.

Compression ultrasound is the ideal tool for follow-up examinations since it is noninvasive and can be standardized by a strict protocol. Therefore, an exact documentation of residual thrombus material is possible, which can be taken into account when the risk of recurrent thromboembolism is assessed [16]. CDS is advantageous over compression US because it measures peak systolic velocity changes and may help quantify minimal flow changes in DVT patients.

This study's results demonstrated that reductions were observed in pain and swelling in patients with DVT treated by intravenous infusion of unfractionated heparin and bed rest, subcutaneous administration of LMWHs one dose a day, and pneumatic compression. No statistically significant increase was determined for the Lowenberg test of the diseased leg between days 0 and 7 in the intravenous infusion of unfractionated heparin and bed rest group. A statistically significant decrease in the degree of leg swelling and increased volume flow through the deep veins of the calf and thigh were observed in the groups on low-molecular-weight heparin and pneumatic compression (group D) and intravenous infusion of unfractionated heparin and bed rest (group A). After three days, measurable edema disappeared entirely in the low-molecular-weight heparin and pneumatic compression group and a reduction of the circumference of the leg with DVT was seen. During the seven-day period, severe events were not observed.

The present study may have a few limitations; the number of patients is small and the follow-up duration short (seven days). Therefore further studies are needed on larger samples and the follow-up time should be as long as possible.

Conclusions

We conclude from this study that intravenous infusion of unfractionated heparin and bed rest, subcutaneous administration of LMWHs one dose a day, and pneumatic compression of patients with DVT lead to a faster reduction of leg swelling and pain and increased volume flow through the deep veins of the calf and thigh. During the seven-day period, severe events were not observed.

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