Compression therapy for acute deep venous thrombosis – a double-edged intervention

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ABSTRACT

Objective
To investigate the effect of compression therapy on symptoms and thrombus fate in acute DVT.

Methods
Medical compression stockings (MCS) were compared with placebo stockings (Non-medically Active Reference Stockings, NARS) in patients with popliteo-femoral DVT. Treatment was started immediately upon diagnosis and pursued for 28 days. Thereafter, all patients were wearing MCS. Endpoints were pain, edema, and ultrasound thrombus regression.

Results
Thirty-one patients completed the trial. Within the first 24h, pain on VAS (0 mm=no pain, 100 mm = maximal pain) decreased from 50 mm (±24) to 34 mm (±21) with MCS and from 53 mm (±17) to 49 mm (±17) with NARS (p <.001). After the first day, pain vanished at the same rate in either group. Pain assessed with a provocation test and edema decreased similarly in either group. Thrombi occluded the popliteal and femoral vein lumen at baseline and after 14, 28, and 40 days by 71% (±20), 63% (±20), 59% (±21) and 43% (±29) in the MCS group, respectively, and by 74% (±25), 49% (±28), 38% (±28), and 21% (±24) in the NARS group. The respective decreases from baseline were statistically different between groups at day 14 (p = .024), day 28 (p = .006), and day 40 (p = .082). Safety concerns led to stopping the trial.

Conclusion
Compression therapy started immediately after diagnosis leads to a more pronounced first day pain reduction than treatment with placebo stockings. In contrast, subjective benefit was accompanied by impairment of thrombus resolution.

INTRODUCTION

The typical clinical features of acute deep venous thrombosis (DVT) are calf pain and edema. They are usually managed with either bed rest combined with leg elevation and local treatment or deliberate ambulation combined with leg compression started immediately upon diagnosis.[1-6] The relative merit of these strategies has not been clearly established.

The late sequel of DVT is the post-thrombotic syndrome (PTS) which develops in up to half the patients who suffer a first popliteo-femoral DVT.[7-11] MCS reduce the incidence by about 40%. It is unknown when compression should be started and what its mode of action is.[10-13]

We hypothesized that leg compression would speed up clearance of symptoms in association with enhanced thrombus resolution.

STUDY DESIGN, PATIENTS AND METHODS

Study design
Investigator-initiated, multi-center, randomized, single-blind, placebo-controlled trial with a primarily explorative design. Comparison of MCS with placebo stockings (Non-medically Active Reference Stockings, NARS), either worn for 28 days.

Endpoints
Pain, swelling, and ultrasound documented change of thrombus load.
Inclusion criteria: First, symptomatic, popliteo-femoral DVT diagnosed by compression ultrasound.
Exclusion criteria: Treatment with anticoagulants or leg compression >1 day, clinical signs of pulmonary embolism, superficial phlebitis; signs of chronic venous insufficiency (C4 or higher); inability to walk, contraindication to heparin, phenprocoumon or leg compression; age <18 years, known pregnancy, life expectancy <6 months; consent denied.

Anticoagulant treatment
Tinzaparin (Innohep®), 175 IE/kg b.w., started immediately upon diagnosis and continued until the simultaneously started phenprocoumon had brought the INR to >2 on two consecutive days, but for at least 6 days.

Compression treatment
Calf-length MCS (Sigvaris 503®, ankle pressure 23–32 mmHg) or NARS, especially knitted to yield a texture indistinguishable from the MCS (Ganzoni France SA). MCS use in either group after day 28.

*RESTAT: **R**ole of graduated **E**lastic Stockings for the **T**reatment of **A**cute deep venous **T**hrombosis

Visits: Baseline; trial period: days 1, 3, 9 (±1), 14 (±1), and 28 (±1); follow-up: days 40 (±1) and 90 (±2).

Clinical assessment
Daily recording of hours stockings were worn and number of steps (pedometer). At each visit: rating of leg pain with two tests: VAS (0 to 100 mm with 100 indicating the most unfavorable ruling); assessment of calf pain provoked with an inflatable cuff (Lowenberg test)[14]; measurement of minimal and maximal leg circumferences of both legs (tape).

Ultrasound assessment
Color-coded duplex ultrasound examinations performed at baseline and days 14, 28, and 40. Proximal thrombus end measured from the sapheno-femoral junction (SFJ). Thrombosis load quantified on transverse sections taken 10 cm below the thrombus tip and at the level of the popliteal crease. The surface areas of the main vein as well as of adjacent parallel subfascial veins were recorded. The area of thrombosis was determined after full vein compression with the ultrasound probe. Thrombus load was defined as the proportion of the femoral and popliteal veins' total incompressible surface areas.

Statistical analysis
A power analysis performed on the basis of previous studies[2,4] gave a number needed to include of 30 per group with a power of 0.8 and a two-tailed α-error of 0.05. An interim analysis was performed as half the patients concluded the trial period with MCS or NARS treatment. Patient characteristics were compared using Chi square and t-tests (paired comparison within groups, tests for independent samples for comparison between groups). MANOVA was calculated for change over time and for group differences.

RESULTS

Patient characteristics are given in *Table 1*, data on anticoagulant treatment, compliance with stockings, and walking performance in *Table 2*. All patients were mobile at start of treatment and remained so for the whole study period.

Pain
At baseline, patients rated spontaneous pain on VAS at 51 mm (±21) *(Figure 1)*. Within the first 24 hours, pain decreased significantly (T = 4.0, p <.001). With MCS, the level decreased from 50 mm (±24) to 34 mm (±21); with NARS it lessened from 53 mm (±17) to 49 mm (±17) (T = 2.5, p =.018). On day 3, the mean pain level had decreased to about half of the initial value and the difference between groups had vanished. The threshold cuff pressure provoking pain was 52 (±33) mmHg lower at the calf of the leg with DVT than at the healthy leg *(Figure 2)*. After 3 days, susceptibility to pressure had decreased to 29 mmHg (±29) (T = 4.2, p <.001) with no difference between treatment groups (F = 0.4, p =.784).

Swelling
Differences of ankle and calf circumferences between the legs with DVT and the contralateral legs are depicted in *Figure 3*. Swelling decreased at the same rate with either treatment, had improved significantly after 3 days (T = 4.6, p <.001) and disappeared by the end of the treatment period.

Ultrasound course of thrombosis
Thrombi had reached the groin in 4 cases, ended in Hunter's channel in 1 case, and in between in 26 cases.

Dissolution from the tip down was the same in both groups. The tips' distance from the sapheno-femoral junction increased from 17.0 cm (±12.9) to 21.3 cm (±14.8) (T = 3.6, p =.001). *The veins' total cross sectional area* decreased from 92 mm^2 (±38) to 74 mm^2 (±40) at 28 days (T = 3.8, p =.001) with no difference between treatment groups.

The proportion of thrombus on vein cross-sections decreased with time in both groups (F = 17.7, p <.001) yet to a larger extent in the NARS group *(Figure 4)*. Thrombi occluded the popliteal and femoral vein lumen at baseline and after 14, 28, and 40 days by 71% (±20), 63% (±20), 59% (±21) and 43% (±29) in the MCS group, respectively, and by 74% (±25), 49% (±28), 38% (±28), and 21% (±24) in the NARS group. The respective decreases from baseline were statistically different between groups at day 14 (p =.024), day 28 (p =.006), and day 40 (p =.082). Safety concerns led to ending the trial.

Table 1.
Patient characteristics

		NARS	MCS	P
Characteristics	Patients	13 (42%)	18 (56%)	
	Women	7 (54%)	11 (61%)	.686
	Age	59 (+/- 14)	65 (+/- 14)	.204
Cause of DVT	Secondary*	7 (54%)	7 (39%)	.409
	Idiopathic	6 (46%)	11 (61%)	
Duration of symptoms (days)	Probable symptoms	5.2 (+/- 3.5)	5.5 (+/- 3.8)	.797
	Definite symptoms	2.6 (+/- 3.2)	3.1 (+/- 3.0)	.659
Leg circumference difference (cm)	Ankle	1.0 (+/- 1.0)	1.9 (+/- 2.2)	.170
	Calf	2.5 (+/- 1.9)	2.6 (+/- 2.4)	.933
Extension of DVT (cm from groin)		18 (+/- 14)	16 (+/- 12)	.766
Proportion of vein surface with thrombus (%)	10 cm below tip	76 (+/- 27)	73 (+/- 17)	.709
	Popliteal	69 (+/- 25)	73 (+/- 23)	.670

*Trauma 5, surgery 2, long journey 2, oral contraceptives 4, plasmocytoma 1

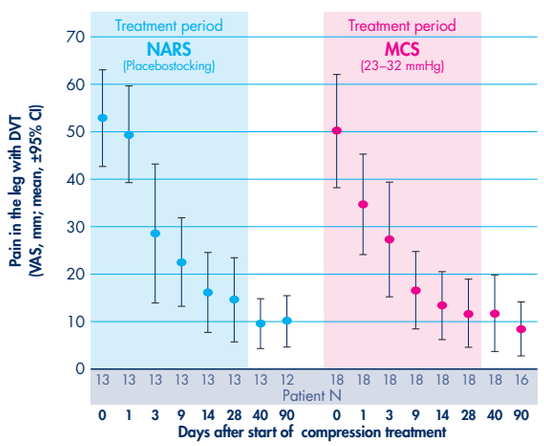
Table 2.

Control of anticoagulation, compliance with stockings and walking performance

		NARS	MCS	P
	Tinzaparin, days (MD, range)	7 (5–15)	8 (4-26)	.568
Prothrombin time	Number of tests between cessation of tinzaparin and day 28	5.2 (+/- 3.6)	4.5 (+/- 1.7)	.566
	Percent INR 2.0–3.0	77.8 (+/- 22.7)	86.2 (+/- 16.6)	.312
Stocking use (hours per day)	Day 1–3	16.8 (+/- 4.2)	14.3 (+/- 5.6)	.257
	Day 4–14	15.7 (+/- 4.6)	13.2 (+/- 3.2)	.128
	Day 15–28	15.1 (+/- 4)	13 (+/- 3.3)	.161
Walking performance (steps per day)	Day 1–3	7230 (+/- 4650)	5660 (+/- 4520)	.405
	Day 4–14	6940 (+/- 3340)	6980 (+/- 4730)	.981
	Day 15–28	6930 (+/- 3580)	7790 (+/- 4230)	.610

Figure 1.

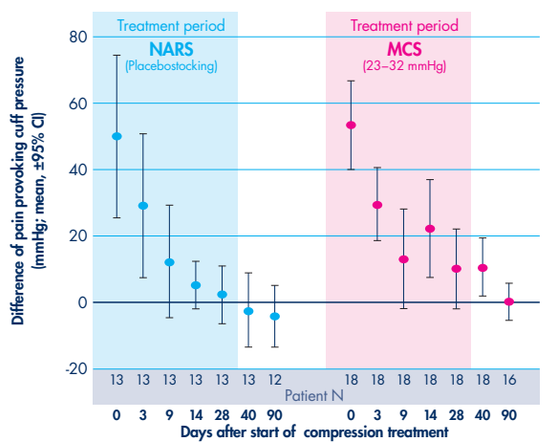
Course of spontaneous leg pain (VAS)



Course (ANOVA multivariate, day 1–28)		F = 20.7	p <.001
Group effect (ANOVA multivariate interaction, day 1–28)		F = 1.3	p = .278
First significant change (paired t-test):	day 1	F = 4.0	p < .001
Differences between groups (t-test):	day 1	F = 2.5	p = .018
Differences between groups (t-test):	day 3–90	None	

Figure 2.

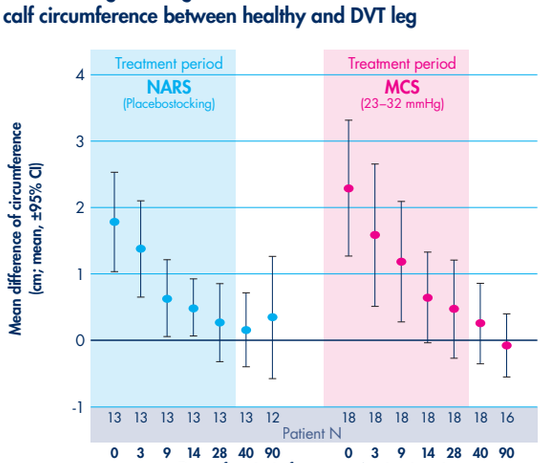
Course of provoked pain (Lowenberg test): Difference of pain provoking cuff pressure between healthy and DVT leg



Course (ANOVA multivariate, day 1–28)		F = 13.6	p <.001
Group effect (ANOVA multivariate interaction, day 1–28)		F = 0.4	p = .784
First significant change (paired t-test):	day 3	T = 4.2	p < .001
Differences between groups (t-test)		None	

Figure 3.

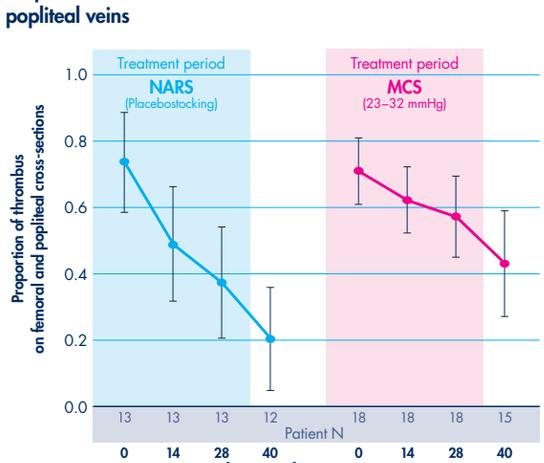
Course of leg swelling: Difference of mean ankle and calf circumference between healthy and DVT leg



Course (ANOVA multivariate, day 1–28)		F = 13.1	p <.001
Group effect (ANOVA multivariate interaction, day 1–28)		F = 1.0	p = .447
First significant change (paired t-test):	day 3	T = 4.6	p < .001
Differences between groups (t-test)		None	

Figure 4.

Proportion of thrombus on cross-section of femoral and popliteal veins



Course (MANOVA multivariate, day 1–28)		F = 17.7	p <.001
Group effect (MANOVA multivariate interaction, day 1–28)		F = 4.3	p = .024
First significant change (paired t-test):	day 14	T = 4.4	p < .001
Differences between groups (t-test):	day 1–14	T = 2.4	p = .024
	day 1–28	T = 3.0	p = .006
	day 1–40	T = 1.8	p = .082

DISCUSSION

Treatment with LMWH and oral anticoagulants has been consistently performed in our study. However, anticoagulant therapy neither improves symptoms nor the fate of thrombi. Leg compression combined with ambulation leads to rapid clearance of pain and entered into recent recommendations.[15,16] Yet, whether its success should be attributed to compression or to deliberate ambulation is ignored. Furthermore, it is not clear whether the benefit is due to enhanced thrombus decomposition or merely to decreased venous congestion. We therefore investigated the role of leg compression per se with the hypothesis that the anticipated subjective benefit would be paralleled by faster and/or more important thrombus clearance. The trial period was limited to 4 weeks as continuation with a placebo stocking was considered inappropriate in view of established long-term benefit of MCS for the prevention of the PTS.[7-10]

Confirming our hypothesis, immediate leg compression reduced pain to a larger extent than placebo treatment. The benefit has disappeared by the third day. Contrary to our expectation, MCS did not expedite thrombus regression but turned out to impede it. How could this be explained? Vein thrombosis is associated with a systemic inflammatory reaction probably set off in the tissues where thrombosis began.[17-19] In an animal model, antiserum induced leucopenia prevented inflammation in the wall of the thrombus harboring vein and led to wall fibrosis within a few days.[20] We may speculate that early calf compression modifies this beneficial systemic inflammation in a negative sense, i.e. hindering thrombus degradation in areas remote of where compression was applied.

Two studies adressed the role of early use of compression and documented a more rapid reduction of pain and swelling as compared with no compression. One study found the immediate application of stockings associated with a trend to more vein segments recanalized on ultrasound images.[12] The other study found no acceleration of thrombus regression when multilayer bandages were applied for the first 7 to 14 days.[13] Neither study addressed the question of a potential disadvantage of early institution of compression.

The number of patients enrolled is smaller than required by the power analysis because safety concerns asked to end the trial before target accrual. Interim analysis showed that the subjective benefit was not associated with an accelerated thrombus disappearance but had turned into the contrary by 38 percentage points (thrombus resolution 17% with MCS versus 49% with NARS). For safety reasons, recruitment was stopped since incomplete thrombus removal is a recognized risk factor for recurrent thrombosis[21,22] and the post-thrombotic syndrome[23,24]. As the differences of either endpoint had already reached statistical significance at study closure the premature end is not a major shortcoming.

In conclusion, immediate application of a MCS after diagnosis of DVT leads to a short-lasting benefit on pain but leads to a reduction of ultrasound regression of thrombi when compared with placebo stockings. Evidence suggests that compression stockings are prescribed to prevent the threatening PTS. On the basis of our results we would struggle to recommend an immediate start of compression but rather suggest waiting until the signs and symptoms waned with anticoagulant therapy reminding the protocols of prior clinical studies.[7,8] Further clinical trials are warranted to define the optimal timing of compression treatment in acute DVT.

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