Therapy of isolated calf muscle vein thrombosis: A randomized, controlled study

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Background: **Treatment of isolated calf muscle vein thrombosis (ICMVT) is controversial. There are no data from prospective, controlled studies. Objective of this article was to compare the efficacy and safety of a short-term course of anticoagulation with compression therapy alone.**

Methods: **We prospectively randomized patients with symptomatic, sonographically proven ICMVT in the soleal and/or gastrocnemial muscle veins in two treatment arms. The first received low-molecular-weight heparin for 10 days at therapeutic dosage (nadroparin 180 anti-activated factor X units once daily) and compression therapy for three months, and the second received compression therapy alone. Primary efficacy endpoint of the study was sonographically proven progression of ICMVT into the deep veins and clinical pulmonary embolism (PE) as confirmed by objective testing. Secondary efficacy and primary safety endpoints were major bleeding, death not due to PE, and complete sonographically proven recanalization of the muscle vein. We assessed transient and permanent risk factors for venous thromboembolism.**

Results: **One-hundred seven patients were finally ruled eligible for evaluation: 89% outpatients, 11% hospitalized patients. In the heparin group (n = 54) progression to deep vein thrombosis (DVT) occurred in two patients (3.7%), in the group compression therapy alone (n = 53) progression to DVT occurred in two patients (n.s.). No clinical PE and no death occurred. Thrombus recanalization after 3 months was not statistically significant different between the two study groups. No major bleeding occurred.**

Conclusion: **The data do not show superiority of a short-term regimen of low-molecular-weight heparin and compression therapy in comparison with compression therapy alone in patients with ICMVT in a rather low-risk population. (J Vasc Surg 2010;52:1246-50.)**

Isolated calf muscle vein thrombosis (ICMVT) is defined as isolated thrombosis in the soleal and gastrocnemial calf muscle veins without involvement of the deep stem veins. It has been a known entity for 30 years,[1] but it is more frequently diagnosed since the shift from venography to venous compression ultrasound.[2-4] The natural history of isolated calf muscle thrombi has not yet been fully elucidated. ICMVT has been suggested as being the first step in the natural course of deep vein thrombosis (DVT) and as well as in symptomatic pulmonary embolism (PE),[5,6] but there is a high likelihood of spontaneous regression. Therefore, treatment of ICMVT is controversially discussed in terms of kind of treatment and duration.[7] Based on a prior cohort study,[8] we hypothesized that a 10-day course of therapeutic low-molecular-weight heparin (LMWH) could be superior to compression therapy alone. We tested this hypothesis by means of a randomized, controlled study.

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METHODS

Study participants. All patients presented in the vascular unit of University of Dresden Medical School with clinical complaints in the lower extremity and suspect of venous thrombosis.

Inclusion and exclusion criteria. We included consecutive patients presenting with symptomatic (less than 14 days), sonographically proven acute ICMVT in the gastrocnemial and/or soleal muscle veins prospectively into the study. Exclusion criteria were: sonographical-proven DVT in the peroneal or tibial posterior veins and in the proximal venous segments, symptomatic PE, previous ICMVT and remaining thrombotic material, known heparin hypersensitivity, renal insufficiency and serum creatinine level above 180 μmol/L, malignant hypertension, active, clinically significant bleeding, cerebral hemorrhage, recent brain, spinal, ophthalmologic surgery, fibrinolysis within the last 24 hours, active peptic ulcer disease, acute bacterial endocarditis, a known familial bleeding disorder, all other indication for anticoagulant therapy, life expectancy <3 months, <8 years of age, and missing written informed consent.

Study design. Patients were randomized in two study groups (block randomization in blocks of 10 according to a randomization table): 180 antiXa u/kg BW nadroparin (Fraxodi) once daily for about 10 days and compression therapy with graduated class-II-calf stockings for 3 months or compression therapy with graduated class-II-calf stockings for 3 months alone. Therapy was started immediately after diagnosis. If indicated for other reasons, prophylactic dosage of heparin was allowed to be continued. Patients

were followed by clinical and ultrasound examinations at day 3, days 10-12, after 4 weeks, and 3 months.

Examinations. All examinations were performed in our vascular diagnostics unit. At baseline examination, we assessed the following acquired risk factors for thrombosis: age, previous venous thrombolic events, trauma, and/or surgery 4 weeks before inclusion, active cancer, immobilization for more than 3 days in the 2 weeks before inclusion, use of oral contraceptives, hormone therapy, pregnancy, and family history of venous thromboembolism (VTE).

Initial laboratory examination included PTT, INR, hemoglobin, hematocrit, platelets, and creatinine. Platelet control was performed on days 10-12 to exclude heparin-induced thrombocytopenia type II. At follow-up examination, all study participants were asked about symptoms of VTE.

Baseline and follow-up diagnostic of ICMVT was performed in our vascular diagnostics unit using venous compression ultrasound according to a standardized examination protocol including the calf muscle veins. The protocol was validated in a safety study of over 1023 patients with negative ultrasound and a failure rate of 0.3% after 3 months.[9] Ultrasound was performed at inclusion into the study, at day 3, days 10-12, after 4 weeks, and 3 months. With the patient supine, the following venous segments were examined with B-mode compression ultrasonography: common femoral vein, proximal part of the great saphenous vein, deep femoral vein, and superficial femoral vein. After this, the study participant had to sit up with legs hanging down. In this position, the following segments were examined with B-mode compression sonography: popliteal vein, proximal part of the small saphenous vein, confluence segment of the posterior tibial and peroneal veins, proximal and distal parts of the tibial posterior and peroneal veins, lateral and medial gastrocnemial muscle veins, lateral and medial soleal sinusoids of the proximal and distal calf, and distal parts of the great and small saphenous veins. ICMVT was defined as a lack of compressibility of one or more segments of either the gastrocnemial or the soleal muscle vein. Progression into the deep veins was defined if initially unaffected segments of the popliteal, tibial posterior, or peroneal veins could not be compressed with the ultrasound globe. In cases of cinically suspected PE, a computed tomography (CT)-scan was scheduled. Recurrent ICMVT was defined as sonographically proven incompressibility in segments of muscle veins initially unaffected. Complete recanalization in the follow-up was defined if a complete compressibility of muscle veins previously defined as thrombotic was seen. Major bleeding was defined as a drop of hemoglobin of >2 mmol/L, the need of transfusion of 2 U packed red cells, and joint, retroperitoneal, or cerebral hemorrhage. In cases of death, the cause of death was confirmed from the death certificate or by necropsy.

Endpoints. Primary efficacy endpoint of the study was sonographically proven progression of ICMVT into the deep veins and clinical PE as confirmed by objective testing. Secondary efficacy and primary safety endpoints were as follows: (1) major bleeding, defined as drop of hemoglobin >2 mmol/2 mg/dL, transfusion of two packed red cells, retroperitoneal, joint or cerebral bleeding, (2) death not due to PE, and (3) complete sonographically proven recanalization of the muscle vein.

Ethics. The study protocol was approved by the institutional ethics committee of the University of Dresden Medical School, Dresden, Germany. Written informed consent was obtained from all participants.

Statistical methods. Sample size calculation was based on our cohort study, conducted in 2000, including 52 patients with therapeutic nadroparin and 32 patients with compression therapy in which a progression to DVT in the compression therapy group of 25% comparing with 0% in the heparin group was revealed (8). Calculating a reduction of propagation into the deep veins on heparin from 25% to 5%, 54 patients in each treatment group are required for a two-sided test with $\alpha = 5\%$ and $\beta = 10\%$ (StatXact-4-statistical software, Cytel Software Corporation, Cambridge, Mass).

Differences between patient characteristics and outcomes were calculated by the Mann-Whitney test and the two-sided Fisher exact test (release 11.0.1 statistical software; SPSS Inc, Chicago, Ill), as appropriate. *P* values <.05 were considered as statistically significant.

RESULTS

Patients. We included 109 patients in the study (40 male/69 female; mean age, 55 years). All patients presented with isolated calf pain. Of these, 55 had been randomized into the low molecular weight heparin (LMWH) group, 54 into the group with compression therapy alone. We diagnosed 40 ICMVT in the gastrocnemial muscle veins (37%), and 69 MVT in the soleal muscle veins (63%). Ninety-one patients presented as outpatients (89%) and 12 patients as hospitalized patients (11%). The analysis of the patient characteristics and the different risk factors for thrombosis are shown in Table I according to treatment arms. The patient characteristics between the two study groups were calculated statistically as not significantly different with exception of statistically significant more recent surgery or trauma in the group compression therapy. Two patients were regarded as study dropouts due to unwillingness to present at follow-up examinations, one in every patient group. Therefore, 107 patients were finally available for evaluation: 54 in the LMWH group and 53 in the group compression therapy without therapeutic LMWH.

Outcomes. In both treatment groups, progression into the deep stem veins occurred in two patients (3.7%, n.s.). In the heparin group, a 42-year-old female patient with soleal thrombosis showed symptomatic DVT into the peroneal veins 10 days after stop of the anticoagulation, and a 39-year-old male patient with gastrocnemial thrombosis showed asymptomatic progression into the popliteal vein 18 days after termination of anticoagulation. In the group compression therapy, only a 61-year-old male patient with

Table I. Characteristics and risk factors

	Therapeutic nadroparin (n = 54)	*Compression therapy, no therapeutic nadroparin (n = 53)*	P *value*
Sex (m/f)	24/30	15/38	.083
Age (MW)	54 (+/−15)	57 (+/−14)	.39
Soleal thrombosis	35 (65%)	43 (81%)	.058
Gastrocnemial thrombosis	19 (35%)	10 (19%)	.058
Permanent risk factors			
Family history VTE	13 (24%)	7 (13%)	.15
Hormone therapy	5 (9%)	6 (11%)	.73
Cancer	1 (2%)	4 (7.5%)	.16
Previous VTE	11 (20%)	11 (21%)	.96
Oral contraception	7 (13%)	4 (7.5%)	.36
Factor-V-Leiden	3 (5.55%)	4 (7.54%)	.92
Prothrombin mutation	1 (1.85%)	0	.60
Protein C deficiency	0	0	
Protein S deficiency	1 (1.85%)	3 (5.66%)	.58
AT III deficiency	0	0	
Transient risk factors			
Immobilization	7 (13%)	12 (23%)	.19
Recent travel	8 (15%)	6 (11%)	.59
Pregnancy	0	0	
Trauma/surgery	11 (20%)	25 (47%)	.03

VTE, Venous thromboembolism.

soleal thrombosis showed asymptomatic progression into the popliteal vein 8 days after inclusion into the study, and an 82-year-old female patient with soleal thrombosis showed asymptomatic progression into the peroneal veins 31 days after inclusion. All characteristics of patients with thrombus progression are given in Table II. No clinical PE, no death, and no major bleeding occurred. No recurrent isolated MVT was seen in any patient in follow-up sonography. Thrombus recanalization was seen in 66% in the heparin group and in 60% in the group without anticoagulation therapy (n.s.) (Table III).

DISCUSSION

This study represents the first randomized trial on therapy of symptomatic isolated calf muscle vein thrombosis. We tested the hypothesis that a short course of therapeutic LMWH could be superior to compression therapy alone.

ICMVT is a common finding, well detected by venous compression ultrasound.[10] In a trial on flight-associated thrombosis, we could show an incidence of 10/1000 asymptomatic ICMVT in a month in a cohort of nontraveling controls performing compression ultrasound at inclusion and 3 to 4 weeks after.[11] We conclude that the incidence of ICMVT is 100 times higher than it is known for symptomatic DVT.[12,13] We assume that most of these small thrombi disappear completely via natural lysis, but a fraction will develop as symptomatic with a potential of progression.[14]

ICMVT has been associated with progression into the deep stem veins as well as to symptomatic PE.[7,8] Whether ICMVT should be treated at all, and if so which treatment regimen is appropriate, remains highly controversial. MacDonald and coworkers followed symptomatic ICMVT with ultrasound controls. They proved a progression rate from ICMVT to proximal DVT of 3% in a 3-month follow-up in a cohort followed by duplex sonography without any treatment at all.[15] However, as a weakness of this study, the investigators could complete the 3-month follow-up in only 65% of the included patients and the mortality during follow-up was very high (12%). The incidence of death from PE remained uncertain because autopsy was not performed.

A further study published by Gillet and coworkers showed in 18.8% of 128 patients with symptomatic ICMVT at least one VTE recurrence in a midterm follow-up (mean, 26.7 months).[16] The authors administered at least 1 month of anticoagulation at a therapeutic dosage. In cases of incomplete recanalization after 1 month, they extended anticoagulation for approximately another 2 months. There are no further data on therapy of ICMVT available at this time.

The results of the present study are in contrast to the results from a prospective cohort study performed at our institution before proving a statistically significant benefit in preventing thrombus progression to the deep stem veins by administering 10 days LMWH to patients.[8] However, comparing the study patient data showed more ongoing risk factors for DVT in the former published cohort study. In the present study, the number of patients with a low risk for VTE was quite high; active cancer was seen in only 4.67% of the study population (21.42% in the cohort study) and ongoing immobilization in 22.64% of the participants (37.5% in the cohort study).

Limitations. A certain influence on the sonographer cannot be completely excluded. Unfortunately, the study represents a rather low-risk population for thrombosis. Only 10.72% of the included participants were hospitalized patients with a higher risk for VTE. Imaging tests for PE were performed only if the patient had symptoms. It is well known that an important percentage of PE cases are subclinical, and this may have an influence toward lower rates of PE diagnosis.

How to treat ICMVT? Obviously, ICMVT is a rather benign finding. Nevertheless, we would recommend to examine the calf veins and to look for these small calf clots. Natural history shows that 90% of DVT are of the ascending type with a potential for embolism.[17] According to the literature, the rate of DVT propagating from distal to proximal is between 0% and 25%. The question is how to identify these patients with a risk for thrombus progression. On the other hand, a risk of overtreatment has to be considered.[18] Therefore, we would like to approve an individual approach. Our data show that in low-risk patients without active cancer, anticoagulation is not necessary. We would recommend in patients with a transient risk a compression ultrasound control 1 week after diagnosis. In a case of propagation to calf-DVT or in the popliteal or femoral veins we would

Table II. Characteristics and risk factors of patients with thrombus progression

	Therapeutic nadroparin 10 days	*Therapeutic nadroparin 10 days*	*Compression therapy, no therapeutic nadroparin*	*Compression therapy, no therapeutic nadroparin*
Sex	Female	Male	Male	Female
Age	42	39	61	82
Soleal/gastrocnemial	Soleal	Gastrocnemial	Soleal	Soleal
Progression	Peroneal veins	Popliteal vein	Popliteal vein	Peroneal veins
Day of thrombus progression after inclusion	20	28	8	31
Progression symptomatic/asymptomatic	Symptomatic	Asymptomatic	Asymptomatic	Asymptomatic
Previous venous thromboembolism	0	0	1	0
Cancer	0	0	0	1
Immobilization	0	0	0	1
Oral contraception	1	0	0	0
Recent travel	0	1	0	0
Trauma/surgery	0	0	0	0
Factor-V-Leiden heterozygous	0	0	1	0

Table III. Outcomes of both study groups

	Therapeutic nadroparin (n = 54)	*Compression therapy, no therapeutic nadroparin (n = 53)*	P *value*
Progression to DVT	2 (3.7%)	2 (3.8%)	.99
PE	0	0	
Death	0	0	
Major bleeding	0	0	
Complete recanalization	36 (66.6%)	32 (60.4%)	.23

DVT, Deep vein thrombosis; *PE,* pulmonary embolism.

treat the patient with anticoagulants. In patients with multiple risk factors or in patients with active cancer alone, we would like to start a short-term regimen of LMWH (for example 4 weeks at a therapeutic dosage), in patients with persistent active cancer, for a longer duration.

A compression therapy with calf stockings class II is able to improve venous outflow. Possibly, there is a benefit for the patient to accomplish freedom from pain earlier. In our study, no patient showed any clinical complaints after 3 months. However, we have no clear evidence for this assumption.

CONCLUSION

We conclude that patients with symptomatic ICMVT without ongoing risk factors do not benefit from short-term anticoagulation. Patients with ongoing risk factors have to be studied again. It is anticipated that short-term anticoagulation for about 10 days is too short in these patients and should be administered for about 4 weeks.

AUTHOR CONTRIBUTIONS

Conception and design: TS
Analysis and interpretation: TS, SMS
Data collection: TS, LB, JB, KH
Writing the article: TS
Critical revision of the article: TS, LB, JB, KH, SMS
Final approval of the article: TS, LB, JB, KH, SMS
Statistical analysis: AR
Overall responsibility: TS

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