

High versus low doses of unfractionated heparin for the treatment of superficial thrombophlebitis of the leg. A prospective, controlled, randomized study

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Background and Objectives. The optimal treatment of superficial thrombophlebitis of the leg is undefined. The main study objective was to assess the efficacy and safety of unmonitored high doses as compared to low doses of unfractionated heparin (UFH) for prevention of venous thromboembolic complications in patients with superficial thrombophlebitis of the thigh.

Design and Methods. Sixty consecutive patients with acute thrombophlebitis of the great saphenous vein, as assessed by ultrasonography, were randomized to subcutaneous injection twice daily of UFH in high unmonitored doses (12,500 IU for one week followed by 10,000 IU) or prophylactic doses (5,000 IU) for four weeks. The rate of asymptomatic involvement of the deep venous system and/or symptomatic thromboembolic events during a six-month follow-up period was assessed and compared between the two study groups.

Results. Six of the 30 patients (20.0%; 95% CI, 7.7 to 38.6) randomized to low-dose UFH developed symptomatic or asymptomatic events as compared to 1 of the 30 patients (3.3%; 95% CI, 0.07 to 17.2) who received high-dose UFH ($p=0.05$ by one-sided Fisher's exact test). No patient experienced major bleeding complications in either group.

Interpretation and Conclusions. The results of this study suggest that in patients with acute thrombophlebitis of the thigh unmonitored high doses of UFH are more effective than prophylactic doses of UFH for prevention of venous thromboembolic complications and do not enhance the risk of bleeding complications.

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In recent studies thrombophlebitis of the great saphenous vein has been shown to be associated with an unexpectedly high risk of venous thromboembolic complications, i.e., extension to the common femoral vein,¹ non-continuous deep vein thrombosis (DVT), and pulmonary embolism (PE).² Several therapeutic approaches have been proposed for patients with this disease, including surgical interventions,³⁻⁵ variable doses of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) followed or not by oral anticoagulant therapy,⁶⁻⁸ and non-steroidal anti-inflammatory drugs.⁸ However, to our knowledge no properly designed comparative trial has been performed addressing the relative efficacy and safety of the various therapeutic strategies. As a consequence, the optimal treatment of thrombophlebitis of the great saphenous vein remains undefined.

We carried out a prospective, controlled pilot study in a consecutive series of patients with acute thrombophlebitis of the great saphenous vein involving the thigh. Patients were randomized to receive high or low doses of UFH for the initial treatment of this disease. The main outcome of the study was to compare the rate of asymptomatic involvement of the deep venous system (as assessed by serial ultrasound examinations at scheduled times until three months after randomization) and/or symptomatic thromboembolic events during a six-month follow-up period. The study was conducted according to the ethical principles stated in the Declaration of Helsinki, and the protocol was approved by the local Ethical Board.

Design and Methods

Study patients

Consecutive patients attending our Institution with symptomatic thrombophlebitis of the great

saphenous vein, as confirmed by ultrasonography, between January 1998 and June 2000 were eligible for the study provided the thrombotic process involved the proximal (i.e., above-knee) venous system.

Patients under 18 years were excluded, as were those with thrombotic involvement of the sapheno-femoral junction (less than 1 cm from the junction), concomitant DVT, previous DVT not followed by complete, ultrasound-confirmed recanalization of the affected veins, clinical suspicion of PE, previous thigh thrombophlebitis, congenital or acquired bleeding disorders, known hypersensitivity or contraindications to heparin, anticoagulant therapy ongoing or required for concomitant diseases, body weight < 50 kg, or pregnancy. All patients meeting the inclusion/exclusion criteria were asked to give their written informed consent before randomization.

Treatment regimens

According to a list generated by a computer, recruited patients were randomly assigned to receive the twice daily subcutaneous injections of UFH either in high doses (12,500 IU for one week, followed by 10,000 IU) or in low doses (5,000 IU) for four weeks. Patients were treated and followed-up on an outpatient basis, and were encouraged to walk early. Systemic and/or local anti-inflammatory drugs were freely delivered.

Initial treatment and follow-up

A regular clinical and ultrasound follow-up was scheduled for all patients until the completion of a six-month period. All patients were instructed to refer to our center on an emergency basis if they experienced a worsening of leg complaints, or clinical manifestations suggestive of DVT or PE.

An ultrasound assessment of the affected saphenous vein, including measurement of the distance from the top of the thrombus to the sapheno-femoral junction was scheduled for day 3 ± 1 , 7 ± 1 , 30 ± 2 and 90 ± 2 according to standard methods,^{7,9-11} and on each occasion the entire proximal deep venous system of both lower extremities was investigated. These assessments were performed by investigators unaware of these patients' treatment regimen. At the end of the six-month follow-up period, all patients underwent a final clinical assessment or were contacted by telephone. During the initial heparin treatment platelet counts were obtained at day 3 ± 1 , 7 ± 1 , 15 ± 1 and 28 ± 2 .

End-points

The main aim of the study was to compare the efficacy of the two treatment strategies regarding

a composite outcome of symptomatic venous thromboembolic complications occurring during the six-month follow-up and asymptomatic DVT occurring during the first three months. Clinically symptomatic DVT was confirmed by compression ultrasound of the proximal-vein system; clinically symptomatic PE was confirmed by ventilation/perfusion lung scanning, followed by spiral CT or pulmonary angiography in the case of indeterminate findings.

In addition, in both treatment groups we evaluated the rate of symptomatic or asymptomatic extension of the thrombotic process involving the great saphenous vein (defined as a progression of at least 2 cm as compared to the screening evaluation) and that of new symptomatic episodes of thrombophlebitis separately during the initial treatment and the follow-up period.

We compared the incidence of major bleeding and that of heparin-induced thrombocytopenia between the two groups during the period of treatment and additional 48 hours. Bleeding was defined as major if it was clinically overt and associated with either a hemoglobin drop of at least 2.0 g/dL or the need for transfusion of 2 or more units of red cells; if it was intracranial or retro-peritoneal; or if it resulted in the permanent discontinuation of anticoagulation. Heparin-induced thrombocytopenia was defined as a decrease in platelet count of at least 50% from baseline or a platelet count below $100\times 10^9/L$ and positivity for heparin-dependent IgG antibodies.

Finally, the overall mortality was reported in each group. The cause of death was investigated by a post-mortem examination or adjudicated according to the opinion of a physician unaware of the aims of the study.

Sample size and statistical analysis

Based on earlier data suggesting a rate of venous thromboembolism of about 30% in patients with thrombophlebitis treated with prophylactic doses of UFH,¹ we estimated that 30 patients per group would enable us to demonstrate a reduction of these complications by 90% ($\alpha=0.05$ and $\beta=0.20$). We used Fisher's exact test for qualitative variables and Student's t-test for quantitative variables.

Results

Patients

Out of 96 consecutive patients attending our center with acute thrombophlebitis of the proximal great saphenous vein, as confirmed by ultrasonography, 28 were excluded because of the following: thrombus involving the sapheno-femoral junction

Table 1. Patients' baseline characteristics.

	Low dose group (n=30)	High dose group (n=30)
Age, yr (mean \pm SD)	62.5 \pm 15.9	61.6 \pm 15.2
Sex (M/F)	12/18	14/16
Patient-doctor delay*, days (median, range)	4.5 (0-15)	4.5 (0-15)
Varicophlebitis, no. (%)	19 (63.3)	18 (60.0)
Distance from the SFJ [^] , cm (mean \pm SD)	8.5 \pm 8.2	7.3 \pm 8.4
Distance from the SFJ < 5 cm, no. (%)	15 (50.0)	18 (60.0)
Risk factors for SVT ^o and VTE (%)		
Age > 65 yr	13 (43.3)	14 (46.6)
History of VTE	4 (13.3)	3 (10.0)
Varicose veins	19 (63.3)	18 (60.0)
Previous SVT ^o	3 (10.0)	6 (20.0)
Active cancer	2 (6.6)	3 (10.0)
Hormone therapy	1 (3.3)	2 (6.6)
Immobilization (> 7 days)	0	1 (3.3)

*Interval between onset of symptoms and patient's referral; [^]sapheno-femoral junction; ^osuperficial vein thrombophlebitis.

(7), concomitant DVT (6), previous thrombophlebitis in the same site (6), suspected PE (3), previous DVT with persistent venous obstruction (3), and oral anticoagulant treatment required for concomitant disease (3). Of the remaining 68 patients, 8 refused to give their consent to enter the trial. Hence, 60 patients were enrolled into the current investigation and were randomly assigned to one of the two treatment regimens. The two treatment groups, consisting of 30 patients each, were fully comparable with regard to demographic and baseline clinical characteristics (Table 1).

Venous thromboembolism

During the treatment period (first four weeks) no patient in the high-dose group (0/30; 95% CI, 0 to 11.6) as compared to 4 patients in the low-dose group (4/30, 13.3%; 95% CI, 3.75 to 30.7) developed thromboembolic complications. The thromboembolic events were asymptomatic in 3 patients (thrombotic extension to the common femoral vein, as detected by repeat ultrasonography during the first week), and symptomatic (non-fatal pulmonary embolism on day 4) in 1. Two of these episodes occurred in patients with varicophlebitis.

During the remaining five months of follow-up, 2 other thromboembolic episodes were registered in the low-dose group (a symptomatic ipsilateral popliteal vein thrombosis, occurring after three months in a patient with varicophlebitis; and a symptomatic thrombosis of the superficial femoral

Table 2. Main study results.

	Low dose group (n=30)	High dose group (n=30)	
Overall VTE [^]	6	1	<i>p</i> =0.05*
VTE during treatment	4	0	<i>p</i> =ns
Overall extension/recurrence of SVT [^]	11	8	<i>p</i> =ns
Ext./recurr. of SVT during treatment	7	3	<i>p</i> =ns
Major bleeding during treatment	0	0	

[^]During the 6-month study period; *by Fisher's exact test (one-sided).

vein, occurring after 14 weeks in a patient with superficial phlebitis involving a non-varicose vessel), as compared to 1 in the high-dose group (thrombosis of the common femoral vein, occurring after eight weeks in a patient with varicophlebitis and a history of previous DVT).

Overall, during the study period the rate of thromboembolic complications was 20.0% (6/30; 95% CI, 7.7 to 38.6) in the low-dose group and 3.3% (1/30; 95% CI, 0.07 to 17.2) in the high-dose group (*p*=0.05 by one-sided Fisher's exact test; *p*=0.10 two-sided) (Table 2).

Extension or recurrence of thrombophlebitis

During the treatment period 7 (23.3%) patients in the low-dose group, as compared to 3 (10.0%) in the high-dose group developed a symptomatic or asymptomatic extension of the thrombophlebitis (*p*=0.15 by one-sided Fisher's exact test). No new episodes of thrombophlebitis occurred in either group.

During the following five months, no patients showed a proximal extension of the thrombophlebitis, whereas 4 (13.3%) patients in the low-dose group and 5 (16.6%) in the high-dose group experienced a documented episode of new superficial vein thrombosis (Table 2).

Other events

No patient died during the six-month follow-up period. No patient experienced major bleeding or heparin-induced thrombocytopenia during the treatment period.

Discussion

The optimal treatment of thrombophlebitis of the thigh is currently undefined. This entity has long been considered as a benign disease, to be managed with local and/or systemic anti-inflammatory compounds. Recent studies, however, have chal-

lenged this concept. They show that thrombophlebitis of the great saphenous vein, when involving the thigh, can extend into the deep vein system and generate the risk of PE in an unexpectedly high rate of patients.^{1,2}

The results of our pilot investigation suggest that, compared to low doses of heparin, high doses of this agent have the potential to reduce the risk of subsequent thromboembolic complications remarkably in patients with acute thrombophlebitis of the great saphenous vein without enhancing the risk of major bleeding. The advantage was particularly evident in the first weeks of treatment, and was further supported by the considerably lower incidence of extension of superficial phlebitis.

As at the time of planning our study LMWHs were not commercially available in Italy, and there was no clear evidence favoring the use of anticoagulant doses of UFH for the treatment of superficial thrombophlebitis of the leg, we elected to use unmonitored high doses of this drug, which made it feasible to treat patients recruited for our investigation at home. This regimen has been successfully investigated in other fields, including the prevention of thromboembolic complications in patients with acute myocardial infarction.^{12,13} We think that for this purpose unmonitored high dose UFH might be conveniently replaced by therapeutic doses of LMWHs, which have many potential advantages over UFH.¹⁴ The choice of prophylactic doses of heparin in the control group was made because at the time of planning our study they were commonly used for this indication.

We used a composite outcome of asymptomatic and symptomatic venous thromboembolic complications. We considered it important to document the asymptomatic involvement of the proximal-vein system because, in patients with previously unaffected deep veins (as the patients recruited in our investigation), the involvement of the popliteal and particularly the common femoral vein (via the sapheno-femoral junction) is an essential requirement for the development of more serious complications, such as fatal or non-fatal PE. It is interesting to note that in the group of patients treated with high doses of heparin, in whom only one symptomatic event developed during the six-month follow-up period, no cases of asymptomatic involvement of the deep venous system were observed during the first three months of follow-up.

The potential limitations of this study are the relatively small sample size, the open nature of the study design, and the lack of standardized criteria for adjudicating the extension of superficial throm-

bophlebitis. Given the lack of guidelines for the treatment of this disease, we decided to perform a pilot study which could provide the basis for subsequent larger clinical trials. The thromboembolic events were adjudicated by an independent panel of physicians, totally unaware of the patients' details and study arm. Extension of superficial thrombophlebitis was a secondary end-point of this study.

In conclusion, the results of this pilot study suggest that in patients with acute thrombophlebitis of the thigh, unmonitored high doses of UFH are more effective than prophylactic doses for the prevention of venous thromboembolic complications and do not enhance the hemorrhagic risk. Further larger clinical trials are necessary to demonstrate conclusively whether this clinical condition should be added to the array of thromboembolic disorders requiring management with full doses of anticoagulant drugs.

Contributions and Acknowledgments

AM, GMA, PP conceived the clinical trial, analyzed the study results, and wrote the manuscript. FV, LS, GC, FR, LM participated in the study design, enrolled and followed-up patients, and critically revised the manuscript for important intellectual content. All the authors gave their final approval of the version to be published.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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PEER REVIEW OUTCOMES

Manuscript processing

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What is already known on this topic

Several therapeutic approaches have been proposed for patients with superficial thrombophlebitis of the leg. The optimal treatment has not been defined.

What this study adds

The study investigates the efficacy and safety of unmonitored high doses as compared to low doses of unfractionated heparin (UFH) in patients with superficial thrombophlebitis of the thigh.

Potential implications for clinical practice

In these patients unmonitored high doses of UFH are more effective than prophylactic doses of UFH for prevention of venous thromboembolic complications without enhancing the risk of bleeding complications.

Vicente Vicente, Deputy Editor