Unsolved issues in etiology and treatment of venous thrombosis

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Treatment for superficial thrombophlebitis of the leg

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Abstract

Background. The optimal treatment of superficial thrombophlebitis (ST) of the legs remains poorly defined. While improving or relieving the local painful symptoms, treatment should aim at preventing deep-venous thrombosis and pulmonary embolism, which might complicate the natural history of ST. Objectives. To assess the efficacy and safety of topical, medical, and surgical treatments in patients presenting with ST of the legs. Search strategy. We searched the Cochrane Peripheral Vascular Diseases Specialized Trials Register (January 2006), the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1966 to January 2006), EMBASE (1980 to January 2006), and we handsearched reference lists of relevant papers as well as conference proceedings. Selection criteria. All randomized trials evaluating topical, medical, and surgical treatments for ST of the legs were eligible. Quasi-random study designs were excluded. Participants were patients with a clinical diagnosis of ST of the lower extremities or objective diagnosis of the thrombus in the superficial vein. Interventions included any treatment to relieve the symptoms and signs or prevent complications of ST such as topical treatments, compression stockings, compression bandages, leg elevation, medical treatments (for example, non-steroidal anti-inflammatory drugs (NSAIDs) or anticoagulants such as heparin), surgical intervention (for example, ligation, vein stripping, crossectomy). Data collection & analysis. Two reviewers assessed the trials for inclusion in the review, extracted the data, and assessed the quality of the studies using the standard scoring sheet developed by the Cochrane Peripheral Vascular Disease Group. Data were extracted independently from the included studies and any disagreement solved by consensus. Main results. Twenty-five studies involving 2509 patients with ST of the legs were included in this review. Pooling of the data and subgroup analysis were not possible given the heterogeneity of the included studies. Moreover, the methodological quality of most of the trials was poor. The study design and method drawbacks as well as the under-reporting of relevant outcomes such as adverse events or venous thromboembolism (VTE), represented an important limit for the clinical validity and generalizability of the results of several studies. Treatment ranged from (low-molecular-weight ) heparin, to anti-inflammatory agents, topical treatment, surgery and a plethora of
other oral, intramuscular, and intravenous treatments. Both low-molecular-weight heparin (LMWH) and NSAIDs significantly reduced the incidence of ST extension or recurrences by about 70% as compared to placebo. Furthermore, LMWH and NSAIDs seemed to have a similar efficacy and safety. However, the studies which evaluated these treatments had a relatively small sample size which did not allow an adequate comparison between LMWH and NSAIDs. Overall, topical treatments improved local symptoms. However, no data were provided on the effects of these treatments on VTE and ST extension. Surgical treatment combined with elastic stockings in ST was associated with a lower VTE rate and ST progression, as compared to elastic stockings alone. In addition, a relatively small study suggested that surgery may have a comparable efficacy and safety profile to LMWH. **Authors’ conclusions.** LMWH and NSAIDs appear as the current best therapeutic options for ST of the legs. While the available data are too limited to make clear recommendations, an intermediate dose of LMWH for at least a month might be advised. Further research is needed to assess the role of NSAIDs and LMWH, the optimal doses and duration of treatment, and whether a combination therapy may be more effective than single treatment. Finally, adequately designed and conducted studies are warranted to clarify the role of topical and surgical treatments.
Background

The term superficial thrombophlebitis (ST) (also known as superficial venous thrombosis), refers to a pathological state characterized by an inflammatory-thrombotic process in a superficial vein. Distinctive clinical findings include pain and a reddened, warm, tender cord extending along the vein. The surrounding area may show signs of erythema (reddening of the skin) and edema (swelling of the tissue).

Superficial thrombophlebitis is a relatively common disease and although its incidence has never been properly determined, it is estimated to be higher than that of deep vein thrombosis (DVT), which is about 1 per 1000 cases (De Weese 1991; Nordstrom 1992). Predisposing risk factors for ST and venous thromboembolism (VTE) are similar and include for instance varicose veins, immobilisation, trauma, postoperative states, pregnancy, the puerperium, active malignancies, auto-immune diseases, use of oral contraceptives or hormonal replacement therapy, advanced age, obesity, and a history of previous VTE (Barrelier 1993; Bergqvist 1986; Chengelis 1996; de Moerloose 1998; Lutter 1991; Samlaska 1990b). Furthermore, the presence of inherited thrombophilia (a disorder where there is a tendency for thrombosis to occur for example, factor V Leiden, the prothrombin 20210A mutation and deficiencies of the natural anticoagulant proteins C and S) in ST suggest a similar pathophysiology as VTE (de Moerloose 1998; Hanson 1998; Martinelli 1999; Samlaska 1990a; Samlaska 1990b).

Traditionally, ST has been considered a relatively benign disease, but several studies have described an association between ST and VTE (Bergqvist 1986; Blumenberg 1998; Bounaumeaux 1997; Chengelis 1996; Jorgensen 1993; Krunes 1999; Lutter 1991; Quenet 2003; Unno 2002; Verlato 1999). In people with a diagnosis of ST, 6% to 44% are associated with (or develop) DVT, 20% to 33% with asymptomatic pulmonary embolism (PE), and 2% to 13% with symptomatic PE (Bergqvist 1986; Blumenberg 1998; Bounaumeaux 1997; Chengelis 1996; Jorgensen 1993; Krunes 1999; Lutter 1991; Plate 1985; Quenet 2003; Skillman 1990; Unno 2002; Verlato 1999). Superficial thrombophlebitis located in the saphenous main trunk seems to have the strongest association with VTE (Bergqvist 1986; Blumenberg 1998; Chengelis 1996;
Jorgensen 1993; Lutter 1991; Quenet 2003; Unno 2002; Verlato 1999). The variations in estimates reported in the literature are probably due to the retrospective character of most studies, the small number of patients included, and the fact that ST was often diagnosed in vascular laboratories, where patients were referred for suspected DVT.

While the estimates of VTE prevalence in patients with ST vary, management of ST should consider the prevention of this scaring complication beyond the mere resolution of local symptoms (Wichers 2005). Conservative management, mainly focussing on the painful symptoms of disease, might therefore be insufficient.

There is no consensus on the optimal treatment of ST in clinical practice. Several therapies have been proposed in literature, including surgical therapy (ligation or stripping of the affected veins), elastic stockings, non-steroidal anti-inflammatory drugs (NSAIDs) which aim to reduce pain and inflammation, and several anticoagulant agents.

It is not clear whether different locations of ST may influence the choice of treatment. The thrombus location in trunks of either the saphena magna or parva may have the highest risk of extension into the deep vein system and thus could require an aggressive treatment, whereas other locations may be associated with a lower risk of extension and thus they may warrant a less aggressive approach.

The aim of this review is to summarize the evidence from randomized clinical trials (RCTs) on the efficacy and safety of topical, medical, and surgical treatments for ST of the leg.

Objectives

To review the evidence on the efficacy and safety of topical, medical, and surgical treatments in patients with ST of the legs.
Methods

Criteria for considering studies for this review

Types of studies

All randomized controlled trials evaluating topical, medical, and surgical treatments for ST of the legs.

Types of participants

Patients with a diagnosis of ST of the lower extremities based on signs and symptoms of ST (i.e. pain, tenderness, induration (hardening of the tissue), or erythema (reddening of the skin) in a superficial vein) and clinical (palpation) and objective diagnosis of the thrombus in the superficial vein.

Types of interventions

Interventions included any treatment to relieve the symptoms and signs, or to prevent complications of ST such as topical treatments, compression stockings, compression bandages, leg elevation, medical treatments (for example, NSAIDs or anticoagulants such as low-molecular-weight heparin (LMWH), surgical intervention (for example, ligation, vein stripping, crossectomy). Each treatment could be compared with another, with placebo or no intervention. Combinations of therapies could be used.

Types of outcome measures

We included RCTs assessing any of the following outcome measures for any of the reviewed interventions.
Primary outcomes
(1) Incidence of complications:
   • PE;
   • associated DVT or progression of ST into DVT.

(The presence of PE or DVT had to be confirmed by an objective test, namely pulmonary angiography, ventilation/perfusion lung scan, or spiral computed tomography for PE, and ultrasonography, venography, or plethysmography for DVT.)
(2) Symptoms (pain).
(3) Signs (for example induration and erythema).
(4) Quality of life (assessed by means of disease-specific and unspecific questionnaires).

Secondary outcomes
(1) Side effects of treatment (for example, bleeding, thrombocytopenia (reduced platelet count), allergic reactions or surgery complications).

Search strategy for identification of studies

This review drew on the search strategy developed for the Cochrane Peripheral Vascular Diseases Group (PVD). The Cochrane PVD Group's Specialized Register has been constructed from regular electronic searches searches of MEDLINE (1966 onwards), EMBASE (1980 onwards), the Cochrane Central Register of Controlled Trials (CENTRAL), and through handsearching relevant journals. The full list of journals that have been handsearched, as well as the search strategies for the electronic databases, are described in the editorial information about the Cochrane PVD Group in *The Cochrane Library* http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/PVD/frame.html.

We searched for RCTs comparing any treatment versus placebo or another treatment, in patients with ST of the legs.
Electronic searches

The Cochrane Peripheral Vascular Diseases Group searched their Specialized Register (last searched 16 February 2007) and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (last searched Issue 1, 2007). For details of the search strategy used to search CENTRAL see Table 1. The authors searched other electronic databases (CINAHL and IDIS) (up to and including January 2006) and also undertook additional searches of MEDLINE (January 1966 to January 2006) and of EMBASE (January 1980 to January 2006). For details of the search strategy used see Table 2 (MEDLINE) and Table 3 (EMBASE).

Searching other resources

We searched reference lists of relevant papers and conference proceedings and we attempted to contact known experts in the field. There was no restriction on language.

Data collection and analysis

Locating and selecting studies

The authors (MDN and IMW) independently reviewed titles and abstracts from the database searches to determine whether the inclusion criteria were satisfied. Decisions regarding inclusion were made separately and results compared. We resolved any disagreement through discussion. We independently reviewed the full text of identified articles, including those where there was disagreement in the initial title/abstract scanning, to ensure that the inclusion criteria were met. We obtained hard copies of the full text of possible trials for studies that fulfilled the selection criteria. We were not blinded to the journal, institution or results of the study. Titles and abstracts of non-English articles were translated into English and assessed for inclusion. We documented reasons for excluding studies and resolved differences by consensus on whether trials met the inclusion criteria. One author (MDN) scanned conference proceedings and identified articles from other sources (experts or reference lists) and
contracted trialists for further information if required. Two authors (MDN and IMW) independently assessed trials for inclusion in the review.

**Critical appraisal of studies**

We assessed the quality of the trials using the standard scoring sheet developed by the Cochrane Peripheral Vascular Disease Group, specifically examining the randomization method (including allocation concealment), whether the outcome was a blinded assessment and whether it included an intention-to-treat analysis. We also determined whether the number of post-randomization losses and exclusions were explicit. Once this information had been gathered, we classified each study into one of the three quality levels: A, B, or C, following the criteria specified in the Cochrane Handbook (Clarke 2003). We used the Jadad scale (Jadad 1996), and the study-quality criteria developed by Schulz and colleagues (Schulz 1995) to assess the quality of the trials, although these scores were not part of the inclusion/exclusion criteria. External validity was defined by characteristics of the participants (inclusion/exclusion criteria; clinical diagnostic criteria; number of participants; age; sex); the interventions (type and modalities of surgical, medical, and topical treatment); and the outcomes.

**Data extraction**

We (MDN and IMW) independently extracted the data from the included studies using an agreed format. We resolved any disagreements by consensus and, if necessary, by involvement of the third reviewer (SM). For any study published twice, we extracted the data from the more complete study. Collected information included methodological quality, characteristics of patients participating in the study, characteristics of the intervention and control groups, and outcome characteristics of every group of participants.
Chapter 8

*Statistical Analysis*

Prior to obtaining the global effect estimators (a balanced mean of the effect in different trials), we carried out where possible a chi square test of homogeneity to establish the presence of statistically significant heterogeneity between trials (P < 0.1). In the presence of homogeneity, we planned to use the fixed effect (Mantel-Haenszel method) and random-effects models to pool and analyze summary effect sizes. Where possible, we presented results as summary relative risk (RR) for dichotomous variables and standardized mean differences (SMD) for all continuous variables. We determined 95% confidence interval (CI) for each estimate.

We carried out statistical analyses using the Review Manager software (RevMan 4.2). Where possible, we analysed by intention-to-treat, including every individual in the randomly assigned group of treatment regardless of whether they completed the treatment or withdrew from the trial.

*Sensitivity analyses*

We planned to perform a sensitivity analysis to explore further the robustness of our results. We aimed to examine the effect of excluding lower quality studies (open-label studies and studies with incomplete follow up) from the analysis. If possible, we repeated the analysis, taking into account factors that could have introduced bias, such as high levels of exclusions which were unbalanced between the groups, or insecure allocation concealment. Any differences were interpreted cautiously and used to generate hypotheses only. Despite this quality assessment, no study was excluded on the basis of quality.
Results

Description of studies

See*: Characteristics of included studies; Characteristics of excluded studies*. The details for each trial are reported in the 'Characteristics of included studies' table*. Twenty-four trials involving 2469 patients were included in the review. In eight studies data were reported for less than 50 patients, in 10 trials for 50 to 100 patients, and in six studies data were available for more than 100 patients. Interventions and comparisons varied largely among the studies. Seven trials included a topical treatment group, three studies a surgical treatment group, ten LMWH, five NSAIDs, eight reported on oral, intramuscular, or intravenous treatment. Most studies reported on the reduction or disappearance of signs and symptoms reduction or disappearance, nine reported on the incidence of VTE, six on ST recurrence or extension, nine on adverse reactions or side effects. Overall 32 studies were excluded from the review. The reasons for exclusion are listed in the 'Characteristics of excluded studies' table.*

Risk of bias in included studies

Details of the methodological quality for each trial are reported in the 'Characteristics of included studies' table.
The study quality varied to a great extent. Four studies were classified as at low risk of bias (quality level A), eight as at moderate risk of bias (quality level B), and thirteen at high risk of bias (quality level C). Allocation concealment was unclear in nineteen studies, adequate in six. Ten studies did not attempt to blind the assessment of the outcomes or did not report whether blinding was used or not, thirteen had a double-blinded, and two a single-blinded outcome evaluation.

*see http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004982/frame.html
Chapter 8

Effects of interventions

Overall we included 24 trials involving 2469 people with ST of the legs were included in this review.

Despite the relatively large number of comparisons found, no chi-square test of heterogeneity was performed since none of the studies evaluated the same treatment comparisons on the same study outcomes. For the same reason, subgroup analysis and sensitivity analysis were not possible. For most of the treatment comparisons, SMD could not be calculated for continuous variables since the standard deviation (SD) of the means were not provided by the studies.

Low-molecular-weight heparin (LMWH)


Both prophylactic and therapeutic LMWH given for 8 to 12 days were associated with a significantly lower incidence of ST extension or recurrence, as compared with placebo (odds ratio (OR) 0.32; 95% CI, 0.16 to 0.65, and OR 0.33; 95% CI, 0.16 to 0.68, respectively) (Stenox Group 2003). Although the differences were not statistically significant, the incidence of VTE may haven been lower both with prophylactic and therapeutic LMWH shortly after treatment (OR 0.25; 95% CI, 0.03 to 2.25, and OR 0.26; 95% CI, 0.03 to 2.34), but not at the end of the 3-month follow-up period (OR 1.23; 95% CI, 0.37 to 4.17, and OR 0.84; 95% CI, 0.22 to 3.21, respectively) suggesting a catch-up phenomenon. No episodes of major bleeding or heparin-induced thrombocytopenia were observed in any treatment group (Stenox Group 2003).

Combined therapy of LMWH plus elastic compression stockings seemed to reduce the incidence of VTE and ST extension or recurrence, compared to elastic stockings alone (OR 0.07; 95% CI, 0.00 to 1.32, and OR 0.07; 95% CI, 0.01 to 0.52), although the former was not statistically significant. In this study, no data were provided on safety outcomes (Belcaro 1999).
Two studies (Gorski 2005; Katzenschlager 2003) randomized patients to topical treatment with heparin-spray gel or LMWH. A non-significant decrease in DVT was found with LMWH (OR 0.27; 95% CI, 0.03 to 2.85), while local symptoms were similarly relieved by both treatments at 21 days (Gorski 2005).

LMWH versus surgical treatment (saphenophemoral disconnection) in one study (Lozano 2003). A comparable reduction of VTE events and a similar safety profile were observed in the two study groups. Surgery seemed to be associated with a lower risk of ST extension or recurrence (OR 0.31, 95% CI, 0.03 to 3.17), although the differences were not statistically significant.

Therapeutic-dose LMWH was evaluated versus NSAIDs in two investigations (Stenox Group 2003; Titon 1994). Fixed-dose LMWH and dose-adjusted LMWH seemed to produce a similar reduction in VTE and ST recurrence relative to NSAIDs. Both these studies were, however, not properly sized for a direct comparison between LMWH and NSAIDs. No major bleeding episodes or cases of heparin-induced thrombocytopenia occurred within either study group. In one of these studies which used placebo as a control group, an indirect comparison between prophylactic LMWH and NSAIDs suggested a non statistically significant reduction in VTE at the end of treatment (OR 0.44; 95% CI, 0.04 to 4.98) (Stenox Group 2003).

A recent study has compared two regimes of LMWH with each other (Vesalio Group 2005). In a head-to-head comparison with 1-month therapeutic-doses, prophylactic-dose LMWH, administered for the same period, lead to a similar reduction in ST extension or recurrence and VTE events (OR 1.21; 95% CI, 0.39 to 3.78) over a 3-month follow-up. In the prophylactic LMWH group most of VTE events (77%) occurred while patients were still on treatment, whereas only 33% of patients on therapeutic-dose LMWH developed VTE during LMWH. This advantage was lost, however, after drug discontinuation with no difference at the end of the study period. No major bleeding or heparin-induced thrombocytopenia events were observed during the study. Local symptoms and signs regressed faster with therapeutic-dose LMWH although the difference was not significant.

Prophylactic-dose intravenous (iv) unfractionated heparin (UFH) was used as comparator treatment in two studies (Belcaro 1999; Marchiori 2002). Relative to elastic stockings alone, prophylactic iv UFH plus elastic stockings was associated with a 86% reduction in ST extension or recurrence (OR 0.14; 95% CI, 0.03 to 0.67), and with a
non statistically significant lower VTE rate (OR 0.08; 95% CI, 0.00 to 1.41) (Belcaro 1999). One study compared high- versus low-dose iv UFH. A non significant 86% reduction in VTE (OR 0.14; 95% CI, 0.02 to 1.23) and a 37% (OR 0.63; 95% CI, 0.21 to 1.88) lower rate of ST extension or recurrence were observed among patients treated with high-dose UFH (Marchiori 2002). There were no episodes of major bleeding and heparin-induced thrombocytopenia in either study group.

Subcutaneous calcium heparin was evaluated in two studies (Belcaro 1989; Belcaro 1990). The combination of elastic stockings plus calcium heparin did not significantly improve the local symptoms and signs as compared to elastic stockings alone. Treatment with calcium heparin was correlated with a faster reduction of the analogue score and the area at maximum temperature than with defibrotide, although the difference was not significant. There were no side effects.

Non-steroidal anti-inflammatory drugs (NSAIDs)
Five studies included a NSAIDs group (Anonymous 1970; Ferrari 1991; Nusser 1991; Stenox Group 2003; Titon 1994). Of these, two compared NSAIDs with placebo (Anonymous 1970; Stenox Group 2003), two with LMWH (Stenox Group 2003; Titon 1994), and two randomized patients to two different NSAIDs (Ferrari 1991; Nusser 1991). The trials that evaluated a NSAID compound versus LMWH have been previously presented (Stenox Group 2003; Titon 1994).

NSAIDs significantly reduced the risk of ST extension or recurrence by 67% (OR 0.33; 95% CI, 0.16 to 0.68), as compared to placebo (Stenox Group 2003). However, there were no differences in the incidence of VTE or in the resolution of local symptoms and signs. While no major bleeding episodes were recorded in any NSAIDs or placebo groups, indomethacin carried a significantly higher rate of side-effects as compared to placebo (OR 3.67; 95% CI, 1.01 to 13.34) (Anonymous 1970).

In one study, oral acemetacin lead a better resolution of the local clinical picture than diclofenac (Nusser 1991). Another trial compared nimesulide to diclofenac sodium (Ferrari 1992). Local symptoms were similarly improved by both treatments. In the group of patients randomised to nimesulide a lower incidence of gastric pain episodes was evident (OR 0.22; 95% CI, 0.02-2.11) (Ferrari 1992), although the difference was not statistically significant.
Topical Treatment

Seven studies included a topical treatment group (De Sanctis 2001; Gorski 2005; Holzgreve 1989; Incandela 2001; Katzenschlager 2003; Nocker 1991; Pinto 1992). The comparison of heparin-spray gel versus LMWH has been described previously (Gorski 2005; Katzenschlager 2003).

One study randomized patients to receive topical Methylthioadenosine or placebo (Pinto 1992). Methylthioadenosine was associated with a non significant reduction in local signs and symptoms relative to placebo.

In a similar way, a significant improvement in the local symptomatology was observed with diclofenac gel (Holzgreve 1989; Nocker 1991), essaven gel (De Sanctis 2001; Incandela 2001), or exhirud oitment (Nocker 1991), as compared to placebo.

Only one study evaluated two different gels, diclofenac gel and etofenak gel (Holzgreve 1989), and showed a comparable efficacy profile of the two topical medications. None of these studies evaluating a topical treatment reported data on VTE or ST extension or recurrence.

Surgery

Three studies included a surgical treatment (Belcaro 1989; Belcaro 1999; Lozano 2003). As described above, one study compared surgery (saphenofemoral disconnection) with LMWH (Lozano 2003). In the remaining two, surgery combined with elastic stockings was compared with elastic stockings alone (Belcaro 1989; Belcaro 1999).

In the first trial, thrombectomy plus elastic stockings with or without venoruton lead to an improvement of the local clinical signs and a greater reduction in the number of veins with ST, as compared to elastic compression bandage alone (Belcaro 1989). There were no cases of DVT in either study-group. In the second trial, ligation of the vein plus elastic stockings was associated with a non significant reduction in VTE events (OR 0.32; 95% CI, 0.06 to 1.62), and ST recurrence or extension (OR 0.42; 95% CI, 0.15 to 1.16), relative to control treatment (Belcaro 1999).
Compared with elastic stockings alone, venous stripping plus elastic stockings decreased the risk of ST extension or recurrence rate (OR 0.07; 95% CI, 0.01 to 0.57), and seemed to be associated with a lower non-significant incidence of VTE (OR 0.35; 95% CI, 0.07 to 1.81) (Belcaro 1999).

Other
Nine studies evaluated an oral (n=6), intramuscular (n=1), or intravenous (n=2) treatment.
Compared with placebo, oral vasotonin was associated with a higher proportions of patients cured or improved (Kuhlwein 1985). The criteria to determine the response to study treatment were not described. Vasotonin seemed to be well tolerated with one case of poor tolerability among patients treated with vasotonin (3%) versus 5 cases (13%) in the placebo arm (OR 0.18; 95% CI, 0.02 to 1.61).
The combination of venoruton, thrombectomy, and elastic stockings versus elastic stockings alone has been discussed above (Belcaro 1989). In the same trial, venoruton combined with elastic stockings lead to an improvement of local symptoms as compared with elastic stockings alone.
One study evaluating oral heparansulphate versus oral sulodexide, suggested a greater decrease in local pain, hitching, and redness in patients receiving oral heparansulphate, than in the group of sulodexide (Messa 1997).
Compared with placebo, oxyphenbutazone reduced by four folds the local tenderness and halved the intensity of pain and erythema (Archer 1977).
Oral vitamin-K antagonist in combination with elastic stockings have been evaluated in one study which suggested a reduction in VTE events (OR 0.08; 95% CI, 0.00 to 1.41), and ST extension or recurrence (OR 0.38; 95% CI, 0.13 to 1.12) with the use of vitamin-K antagonists, relative to the control group treated with elastic stockings alone (Belcaro 1999).
Two studies addressed the use of enzyme therapy versus placebo (Koshkin 2001; Marshall 2001). Enzyme treatment seemed to improve local symptoms although the criteria to evaluate response to study-treatment were not reported.
The efficacy of three doses of desmin has been assessed in one trial (Andreozzi 1996). A better control of local symptoms was obtained with higher doses of desmin without increase in the risk of adverse events.
Discussion

A lot of controversy still exists around the optimal treatment of ST of the legs. The therapeutic approach of ST should aim at the resolution or improvement of the local symptoms, but also, and even more, at preventing the possible extension of superficial vein thrombosis into the deep-venous system (Wichers 2005).

This review summarized data from over 2400 patients with ST of the legs. Most of the studies comparing oral treatment, topical treatment, or surgery did not report about VTE or ST progression or adverse events or treatment side effects. In addition, the methodological quality of these studies was often poor with major study design flaws such as an unclear method of allocation or randomization, the lack of a placebo as control group, or an unacceptably high drop-out rate. All these limitations weaken the clinical applicability of the results and cast doubts over the actual efficacy and safety of these treatment strategies. Compared with placebo or topical treatments, both NSAIDs and LMWH could help in preventing VTE events and ST extension while effectively controlling for local symptoms. When compared to each other, LMWH and NSAIDs seemed associated with a similar reduction in the incidence of VTE and worsening of ST. However, the conclusions of one of the two studies which evaluated LMWH and NSAIDs are hampered by the several methodological drawbacks and the low incidence of VTE relatively to the small sample size. The second study used placebo as control and was not primarily designed nor properly sized for a direct comparison between LMWH and NSAIDs. Thus, these data remain preliminary and further research is required to determine which treatment works better in terms of VTE prevention, and whether a combination may be more effective. Moreover, the benefits of LMWH and NSAIDs have to be balanced against the associated risk of bleeding and gastric complications. None of the studies evaluating LMWH reported major bleeding episodes in patients randomised to LMWH. Non-steroidal anti-inflammatory drug treatment increased by three fold the risk of gastric pain compared with placebo. To date, no study has evaluated NSAIDs versus surgery, whereas one trial directly compared LMWH with surgical treatment showing a comparable efficacy and safety of the two study treatments. Despite the methodological limitations of this study its
results would suggest that a medical approach with LMWH would be as effective and safe as an invasive surgical treatment.

The optimal duration of treatment for ST as well as the best LMWH or NSAIDs regimen to use remain unclear. In the only available head-to-head comparison of two LMWH doses, one month prophylactic LMWH seemed as effective and safe as higher doses over a three month follow-up period. Most of the events in the prophylactic LMWH group occurred while patients were receiving the drug whereas almost two thirds of the events in the therapeutic LMWH arm occurred at drug discontinuation. These data would suggest that a longer therapeutic-dose LMWH would carry a more effective protection against VTE or ST recurrences. This hypothesis is further supported by the data of another study in which LMWH or NSAIDs given for 10 days tended to reduce the incidence of VTE shortly after treatment compared to placebo, although this advantage was not longer evident at the three month follow-up period.

Preliminary data suggest that high-dose UFH can be effective in the treatment of ST. No direct comparison of UFH versus LMWH or NSAIDs has been evaluated. In principle, the use of LMWH may be preferable due to for example to the more predictable response of LMWH which do not require laboratory monitoring as UFH.

**Authors’ conclusions**

**Implications for practice**

The treatment of ST should improve local symptoms while preventing the development of complications such as VTE. Thus, topical treatment does not seem a reasonable options to treat these patients. The most effective approach to ST seem to be represented by LMWH which has been shown to prevent VTE events and the extension or recurrence of ST. In addition, the administration of LMWH does not seem to carry a high risk of bleeding. Although the data are still too preliminary to make any recommendation, an intermediate dose of LMWH for at least a month might be
appropriate. Non-steroidal anti-inflammatory drugs may be an alternative to LMWH, whereas there are not enough data to support surgery or topical treatment as options. Similarly, none of the other oral, intramuscular, or intravenous treatment possibilities evaluated in the clinical studies so far can be recommended for ST management. Although the amount of data regarding surgery is less than for anticoagulation, existing data suggest that surgery may be beneficial regarding local recurrence and extension of thrombosis, allowing for superior symptomatic relief from pain.

Implications for research

Several questions about the treatment of ST remain unsolved. Large and adequately designed RCT are needed to assess the actual role of NSAIDs and LMWH, whether these drugs are actually comparable and whether used in combination they may be more effective and as safe compared with a single treatment. Another important issue to clarify is the duration of ST treatment. The current available data suggest that LMWH for a week is probably too short to prevent VTE in the long term. A prolongation of LMWH or NSAIDs for at least a month might be considered. Whether topical treatment might add some benefit if given in combination with LMWH or NSAIDs remains unclear. Finally, whether treatment needs to be adapted based on the location and the etiology of superficial thrombophlebitis warrants further investigation.

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