Medical management of acute superficial vein thrombosis of the saphenous vein

Sherry D. Scovell, MD, Emel A. Ergul, MS, *and* Mark F. Conrad, MD, MMSc, *Boston, Mass*

ABSTRACT

Objective: Acute superficial vein thrombosis (SVT) of the axial veins, such as the great saphenous vein (GSV), is a common clinical condition that carries with it significant risk of propagation of thrombus, recurrence, and, most concerning, subsequent venous thromboembolism (VTE). Conservative therapy with nonsteroidal anti-inflammatory medication and heat does not prevent extension of thrombus or protect against recurrent or future VTE in patients with extensive SVT (thrombotic segment of at least 5 cm in length). To prevent future thromboembolic events, anticoagulation has become the treatment of choice for extensive acute SVT in the GSV. In spite of this, the dose and duration of anticoagulation in the treatment of SVT vary widely. This review summarizes the evidence from large prospective, randomized clinical trials on the treatment of SVT with anticoagulation (vs placebo or different doses and durations of anticoagulation) with respect to the outcome measures of thrombus extension, SVT recurrence, and future VTE.

Methods: A systematic search was performed using the MEDLINE database to identify all prospective, randomized controlled trials of treatment with anticoagulation in patients with SVT in the GSV. Six prospective, randomized trials were identified that met the inclusion criteria and were reviewed in detail.

Results: Treatment of acute SVT was most commonly managed in an outpatient setting using either low-molecular-weight heparin (LMWH) in four studies or, alternatively, a factor Xa inhibitor in one large multicenter trial. LMWH was associated with a lower rate of thrombus extension and subsequent recurrence, especially when an intermediate dose (defined as a dose between prophylactic and therapeutic doses) was used for a period of 30 days. The full effect of treatment with LMWH on the risk of subsequent VTE remains unclear, as do the optimal dose and duration of this drug. Prophylactic doses of fondaparinux, a factor Xa inhibitor, were found to be beneficial in reducing the rate of thrombus extension and recurrence as well as in reducing the risk of subsequent VTE both during treatment and after cessation of anticoagulation in the short term.

Conclusions: These data suggest that treatment of acute SVT of the GSV with anticoagulation, at doses below therapeutic levels, does offer the benefit of decreased risk of thrombus propagation, recurrence, and, at least in one large randomized clinical trial, subsequent VTE. Future studies to refine optimal dose and duration of anticoagulation to lower the rate of subsequent thromboembolic events and SVT recurrence are needed. (J Vasc Surg: Venous and Lym Dis 2017;■:1-9.)

Superficial vein thrombosis (SVT) is a common clinical condition that affects up to 57% of patients with varicose veins as well as patients without varicose veins who have thrombophilia or malignant disease.[1,2] However, in spite of its clinical frequency, there is wide variability in how patients with SVT are treated.[3,4] This is likely due to a lack of clear conclusions from the available data and to the historic belief that SVT is self-limited with a benign prognosis. In the past, SVT was diagnosed on the basis of clinical signs and symptoms alone and treated conservatively with warm compresses, anti-inflammatory medications, and elastic compression.

From the Division of Vascular and Endovascular Surgery, Massachusetts General Hospital.

Author conflict of interest: none.

Correspondence: Sherry D. Scovell, MD, Division of Vascular and Endovascular Surgery, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114 (e-mail: sscovell@partners.org).

The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2213-333X

https://doi.org/10.1016/j.jvsv.2017.08.016

However, the management of SVT has changed with the advent of venous duplex ultrasound imaging and color flow Doppler. Specifically, duplex ultrasound imaging allows for the accurate diagnosis of SVT. It defines the anatomic location and extent of the thrombus and is used to evaluate for propagation of thrombus over time. Most significantly, it allows evaluation of the deep venous system of the lower extremity to exclude concurrent obstruction.

Directly related to the accuracy of duplex ultrasound imaging, it was discovered that SVT is not a benign clinical process, especially when there is involvement of a superficial truncal vein, such as the great saphenous vein (GSV), and when the thrombus is at least 5 cm in length.[5] In these cases, SVT is associated with a significant risk of venous thromboembolism (VTE) at the time of diagnosis, which has been noted to be as high as 20% in multiple observational studies.[6-10] With short-term follow-up, SVT has been found to be associated with the development of subsequent symptomatic VTE in >8% of patients despite of treatment with anticoagulation.[6] SVT is also associated with a risk of propagation of thrombus within the axial saphenous venous system and extension into the deep venous system by way of the saphenous-deep

venous connections, such as the saphenofemoral and saphenopopliteal junctions or, less commonly, the perforating veins of the limb.[6,9] Finally, SVT may lead to recurrent or new episodes of thrombosis in 2.0% to 6.1% of patients.[11] Particularly, it is SVT in the GSV, especially in the above-knee segment, that is the most concerning for associated propagation of thrombus and has the strongest association with subsequent VTE.[9,12] There are fewer data on SVT of the small saphenous vein, although it is treated in a similar manner.[13]

Acute SVT may be treated by either medical or surgical modalities once it is accurately diagnosed by venous duplex ultrasound examination. Most of the surgical literature, primarily focused on ligation of the saphenofemoral junction and stripping of the saphenous vein, is >10 years old.[14-17] Although there are emerging case reports and small-center studies examining the potential role of early endovenous ablation in acute SVT,[18,19] medical management with anticoagulation has been the main treatment recommended to patients, especially when it is localized to the above-knee GSV with thrombus burden of at least 5 cm in length. Surgical management, including saphenofemoral ligation, is reserved for patients in whom anticoagulation is prohibitive and thrombus is close (within 3 cm) to the junction of the deep veins. For the purpose of this review, medical management with anticoagulation is the focus. The literature during the past 20 years on anticoagulation is notable for multiple clinical trials on this subject. However, as noted in the Cochrane review of SVT, a minority of these trials compared treatment groups with placebo, and none evaluated the same treatment comparisons in terms of dose and duration of treatment on the same study outcomes of subsequent VTE and recurrence or extension of SVT, which precludes meta-analysis.[20]

This review highlights prospective, randomized controlled trials evaluating medical management of SVT with anticoagulation. Doses and duration of anticoagulants are compared to determine the optimal treatment for acute SVT with respect to decreasing future thromboembolic events.

METHODS

A comprehensive literature search was performed to identify all of the randomized controlled trials that evaluated medical management of acute SVT with anticoagulation for the prevention of VTE and the propagation and extension of thrombus. Studies were identified using the MEDLINE database of English-language medical literature from 1980 to February 2015. The key search terms used were *superficial vein thrombosis, treatment superficial vein thrombosis, anticoagulation superficial vein thrombosis, acute superficial vein thrombosis, phlebitis and leg, superficial thrombophlebitis, treatment superficial thrombophlebitis, acute superficial thrombophlebitis, phlebitis leg anticoagulation,* and *anticoagulation superficial thrombophlebitis*. Searches were conducted using the individual words as well as in combination.

Studies were restricted to human and English language, and bibliographies from retrieved studies were also searched for additional manuscripts. Relevant studies were identified using the inclusion criteria of acute superficial thrombophlebitis of the GSV and its tributaries, not involving the deep venous system, confirmed by duplex ultrasound imaging, and treated with medical management. Medical management was defined as anticoagulation in comparison with placebo or nonsteroidal anti-inflammatory drugs (NSAIDs) or anticoagulation in differing doses and durations in prospective, randomized clinical trials. Any publications including SVT with concurrent deep venous thrombosis (DVT) at the time of diagnosis were excluded. Cases of SVT related to venous surgery or endovenous procedures were excluded in addition to those involving superficial migratory thrombophlebitis and suppurative thrombophlebitis. Studies evaluating heparin spray gel and other topical agents were excluded as well. Studies primarily comparing results of medical management with surgical management were excluded, as were studies with fewer than 50 patients, studies in which there was extension of thrombus into the deep venous system at the time of diagnosis documented by duplex ultrasound imaging, and studies in which the diagnosis of SVT was made by clinical examination alone.

Titles and abstracts were screened from the database search to identify studies that met the inclusion criteria. These identified articles were then evaluated in their entirety. Data were then extracted from the articles, including author, title of publication, date of publication, total number of study participants, method of diagnosis of SVT, location of SVT, treatment method (including duration and doses of anticoagulation), and follow-up parameters (such as incidence of recurrent SVT, incidence of extension of SVT, and incidence of subsequent VTE). A total of six studies met the inclusion criteria (Table I). These six studies were ranked according to Sackett's criteria regarding levels of evidence and associated grades of recommendations for published literature.[21] Because of the lack of similar comparisons of dose and duration of anticoagulation as well as outcome measures, a formal meta-analysis of the data was not performed.

RESULTS

Since 1999, there have been six prospective, randomized studies in the literature evaluating the medical management of SVT with anticoagulation meeting the inclusion criteria (Fig). All of these six studies were noted to be either Sackett level I or level II. The first of these studies compared low vs high doses of unfractionated heparin, which is primarily applicable to the diagnosis of inpatient