Supplement to

Vascular Surgery

Official Publication of the
Society for Vascular Surgery®

Volume 52 Supplement S November 2010

A Call to Action: Reducing Venous Ulcers by Fifty Percent in 10 Years

Proceedings of the Pacific Vascular Symposium 6
Kona, Hawaii, November 12-15, 2009

Mosby
www.jvascsurg.org

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CRITICAL ISSUES IN ULCER PREVENTION IN POSTTHROMBOTIC DISEASE

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Postthrombotic syndrome (PTS) is a major source of venous ulcers accounting for an estimated ±50% as causative etiology. A total of 1% to 7% of patients with PTS are estimated to develop an ulcer in 5 to 10 years, but the true incidence is not known as recurrent thrombosis is a major factor in PTS development (grade 1).[1] Recurrent thromboses are known to occur years and even decades later[2,3] making accurate estimation of true PTS and ulcer incidence impossible as a practical matter.

For purposes of this article, we will assume that any reduction in overall incidence of PTS will also result in ulcer prevention as ulcer-specific data is nonexistent. We examine below known and potential avenues of preventing or controlling PTS symptoms.

ANTICOAGULATION

Prevention of recurrent thrombosis will likely reduce eventual ulcer incidence.[4] This rests on proper use of anticoagulation in vulnerable subsets to prevent recurrent thromboses; permanent anticoagulation may be indicated. Predisposing factors for recurrent thrombosis includes unprovoked thromboembolism (grade 1),[1,5] incomplete resolution of initial thrombus (grade 1),[6,7] chronic venous disease (grade 1), thrombophilia,[1,2] obesity, female gender, and age.[2,8] There is some dispute regarding the relevancy of the last four factors in recurrent thrombosis or development of PTS.[9,10] Initial severity of symptoms is a predictor for development of PTS (grade 3).[8,11] A number of newer anticoagulants that are easier to administer, monitor, and regulate are likely to come on stream in the near future. This will likely make it easier to prevent recurrent thromboses. Speedy approval of effective drugs should be encouraged. Several such agents have been shown to be effective in Europe but face delay and hurdles for United States approval.

COMPRESSION

Compression stockings and assist devices[12] have been shown to have prophylactic value in several studies, some extending 5 to 7 years (grade 1B).[1,13-15] A few contradictory results have been reported[16,17] probably due to low power, short follow-up, or variability of compression use including noncompliance. Class I or II stockings are required for effective prophylaxis of PTS after venous thrombosis had occurred, grade 3 evidence[18] and stockings frequently used as prophylaxis against deep vein thrombosis (eg, thrombo embolic deterrent hose) do not provide adequate compression. A high percentage of patients discharged with compression stockings do not use them later.[19,20]

Current practice patterns allow considerable room for improvement in proper prescription, usage, and compliance monitoring.

LYSIS

Lytics, via systemic or catheter route, resolve thrombus,[21] and improve long-term patency[22] (grade 2). Catheter lysis has been shown to preserve valve function and reduce reflux near term[23-26] and improve quality of life at 2 years (grade 3).[27] These surrogate endpoints suggest that PTS incidence may be improved long-term as well. Definitive studies are pending.

Pharmaco-mechanical thrombectomy is currently being evaluated for removal of thrombus and preliminary results have appeared in print.[28-30]

PATHOLOGY

There is broad agreement that the pathology of PTS is combined obstruction and reflux even though available evidence is only grade 2.[31-33] Respective role of reflux or obstruction is undetermined. A large body of work spread over the past century has clearly established the importance of reflux in PTS. Recent grade 3 evidence has ignited interest in the clinical importance of obstruction.[34,35] Substantial clinical relief, including healing of ulceration, was reported in a large series of 528 limbs when the obstructive component was corrected and the reflux (severe in 59% with 42% being axial) was left uncorrected.[36] Conflicting reports have also appeared regarding the relative importance of affected vein segments in these two pathologies (obstruction and reflux). Regarding obstruction, attention has focused on the proximal vein segments (iliac-femoral) and the distal segments (popliteal-tibial); femoral vein occlusion seems to be well-compensated with good collateralization from the deep femoral vein (grade 3).[31,37] Grade 2 and 3 evidence has been presented in support of the importance of proximal vein obstruction either alone or in concert with distal segment in the development of PTS.[35,38-42] However, obstruction of distal vein segments has been related to the development of PTS also (grade 3 evidence).[43-46] Similarly conflicting (grade 3) data has appeared regarding the relative roles of proximal or distal segment reflux[47,48] including the concept of 'gate keeper' valve[44,49-52] in the genesis of PTS symptoms.

We have inadequate understanding of the interaction between postthrombotic obstruction and reflux and their relative importance. Thrombus resolution seems to spare valve function[53] in some instances and reflux seems to occur in previously thrombosed[33] and unthrombosed valve segments as well.[52,54,55] The mechanism of postthrombotic valve reflux seems more complex than initially appears.[52,55,56] Basic science work in this area is sorely needed. Techniques to quantify obstruction and reflux are necessary to understand the pathology and target treatment. It should be noted that current data regarding spontaneous thrombus resolution pertains only to morphologic

recanalization by venography or ultrasound scan without consideration of the quality of such "recanalization."[57] Patency does not equal functional adequacy without hemodynamic obstruction. Venography and duplex scans have poor sensitivity (≤50%) for even morphologic obstruction particularly of the iliac vein segment.[36]

Valve reconstruction can arguably heal ulcers and ameliorate PTS symptoms. Available data is conflicting; certain subsets may benefit.[56] Good efficacy has been shown in repairing valves directly involved in the thrombotic process by one group,[58,59] somewhat less by another,[60] and very little by a third group.[61] Evidence level is grade 3. Because open valve reconstruction is less likely to be used in prophylactic fashion in patients with PTS before actual ulceration (prevention), a noninvasive option needs to be developed. Numerous previous and ongoing attempts to develop a minimally invasive technique have not borne fruit. Relevant in this context is the efficacy of plain nonvalved iliac vein stenting in healing venous ulcers and remitting PTS symptoms (evidence level grade 3).[36]

Saphenous ablation and superficial endoscopic perforator vein surgery are relatively ineffective in PTS (45% cumulative ulcer recurrence at 2 years, evidence level grade 2.[62] Considering that the techniques are minimally invasive, the combination can be used as a temporizing measure to achieve short-term relief. Saphenous reflux is not uncommon in PTS limbs.[63] There is conflicting data on the role of saphenous reflux as a contributor to PTS, evidence level grade 3.[47,64] There is no data on sapheneous ablation alone for ameliorating PTS symptoms, even though it is known to be safe in postthrombotic limbs[65,66] and may play a role in the development of PTS.[48]

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EVIDENCE OF PREVENTION AND TREATMENT OF POSTTHROMBOTIC SYNDROME

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Definition and affliction. Postthrombotic syndrome (PTS) is a chronic condition that is made up of a constellation of clinical signs and symptoms of the lower extremity that develop after deep venous thrombosis (DVT). PTS affects upward of 20% to 50% of patients after DVT and,