Knowns and Unknowns in Managing Postthrombotic Syndrome

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Abstract

Keywords

- postthrombotic syndrome
- iliac vein
- stent
- deep vein thrombosis
- venous ulcer

The postthrombotic syndrome (PTS) is a frequent cause of long-term disability in patients with lower extremity deep vein thrombosis. A broad variety of interventions have been applied to patients with established PTS, including lifestyle, medical, compressive, endovascular, and open surgical therapies. However, the volume of evidence to support many individual elements of care is sparse, and important questions remain that must be answered to enable judicious individualization of PTS care. The purpose of this article is to describe what is known about PTS care elements and to identify important evidence gaps that merit future studies.

Objectives: Upon completion of this article, the reader will be able to identify the treatment options for patients with established postthrombotic syndrome (PTS), and be familiar with the key evidence gaps.

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Postthrombotic syndrome (PTS) develops in approximately 40% of patients after a first episode of symptomatic lower extremity deep vein thrombosis (DVT).¹ The clinical severity and specific manifestations of PTS vary significantly among patients. Patients with PTS commonly experience chronic aching, swelling, fatigue, heaviness, and/or edema of the affected limb, with a minority developing more severe signs (e.g., skin hyperpigmentation, subcutaneous fibrosis), symptoms (e.g., limiting venous claudication), and complications (e.g., leg ulcers). PTS has been shown to limit patients'

daily activities, work productivity, and quality of life (QOL).² In fact, a large prospective cohort study found the presence and severity of PTS to be the leading determinants of a DVT patient's QOL 2 years after the initial episode.³ The same study documented major associated economic costs of PTS to patients and society.⁴

Despite the large numbers of affected patients and the plethora of treatment approaches that are used (including lifestyle, medical, compressive, endovascular, and surgical modalities), physicians acknowledge the presence of more questions than answers in the area of PTS management. There are sparse data to guide physicians in individualizing care. In this article, the author identifies some of the major evidence deficiencies that continue to exist for PTS, with the ultimate goal of stimulating important collaborative research efforts to address these gaps.

What Is Known about Current PTS Treatments

As a first principle of delivering outstanding PTS care, physicians must commit the needed time to properly evaluate PTS patients with the goal of individualizing their care. This means first carefully assessing the medical history and performing a physical exam in a clinic environment, and in most cases synthesizing this information with the results of imaging studies.

Lifestyle Interventions

Studies suggest that obesity is a risk factor for the development of PTS in DVT patients,^{1,5} and also that obese patients are more likely to exhibit progression to increasing levels of severity of chronic venous disease.^{6,7} Therefore, physicians should counsel overweight or obese patients with PTS and help them understand that weight loss (to the extent possible with their PTS activity limitations) may assist in controlling their symptoms and disease progression. However, it is well known that weight loss strategies often fail to achieve weight reduction, and they have not been systematically studied as a way to reduce PTS manifestations. Another common-sense measure that is often applied is to counsel smokers with PTS to stop smoking, and to help them access smoking cessation programs. This is good for general health and might help in preventing some clinical manifestations of PTS, but this also has not been systematically evaluated for PTS management in prospective studies.

Structured exercise therapy has undergone limited evaluation for the management of PTS. In a two-center trial, 43 patients with mild-moderate PTS were randomized to undergo a 6-month program of trainer-supervised exercise therapy versus control treatment consisting of an education session with monthly telephone follow-up. In this study, the mean positive change in venous disease-specific QOL was greater ($p = 0.027$) in the exercise group (6.0 points $\pm$ 5.1 on the VEINES-QOL scale) than in the control group (1.4 points $\pm$ 7.2; $p = 0.027$), likely though not conclusively mediated through reduction in PTS severity ($p = 0.14$ for difference in PTS scale scores).⁸ However, only patients with mild-moderate PTS participated in this study and it is questionable if patients with severe PTS could tolerate this kind of exercise training regimen. Nevertheless, exercise therapy is inexpensive and while most centers do not currently have a PTS exercise therapy protocol in place, this has the potential to be widely applied if effective.

Pharmacological Therapy

Studies have confirmed a strong association between the occurrence of recurrent ipsilateral DVT and development of PTS after DVT.^{1,9,10} Nontherapeutic anticoagulation during the early months after DVT is also predictive of the development of PTS; in one study, PTS occurred 2.5 times more frequently in warfarin recipients who spent less than 50% of their time within the therapeutic INR range.¹¹ Hence, it is reasonable to consider proper anticoagulant therapy for DVT as a “known” measure that reduces PTS risk.¹² However, anticoagulant strategies have not been evaluated for the treatment of patients who have established PTS.

Other pharmacologic agents have been used for the treatment of PTS-associated venous leg ulcers. A Cochrane review evaluated 12 studies of patients ($n = 864$) with venous leg ulcers who were treated with pentoxifylline, concluding that this drug is more effective than placebo for ulcer healing, used with or without compression therapy.¹³ Accordingly, published guidelines suggest the use of pentoxifylline along with wound care

and compression in patients with venous leg ulcers (Grade 2B).¹² Other “venoactive” medications for which limited evidence suggests a benefit for chronic venous disease include micronized purified flavonoid fraction, rutosides, horse chestnut serum derivatives, and escin, but the benefit-to-risk ratio is less clear and therefore these drugs are not supported by strong recommendations for use by published guidelines.^{12,14}

Compressive Therapy

Compression is the mainstay of management of venous ulcers, as clearly shown by the results of multiple randomized trials.¹⁵ For PTS-associated venous ulcers, inelastic compression systems (e.g., short-stretch textiles or multilayer wraps) are generally favored.

However, the evidence is less than compelling for PTS patients who do not have an ulcer. In these patients, elastic compression stockings are commonly prescribed to manage PTS symptoms; however, there is conflicting data from randomized trials and so the frequent use of compression is generally based on the possibility of benefit for some patients coupled with the very low risk of causing harm.^{12,16,17} Compressive therapies such as intermittent pneumatic compression (IPC) have been found in small randomized trials to enhance venous ulcer healing and to alleviate severe edema in some PTS patients.¹⁸ The disadvantages of IPC are its expense and inconvenience, particularly the need to pump for several hours a day. Finally, a portable, battery-powered, venous assist device (VenoWave) was found in one small, placebo-controlled, double-blind, crossover randomized controlled trial (RCT) to provide clinical improvement in patients with PTS.¹⁹ However, it should be noted that all of these studies were quite small, precluding generalization to larger populations of patients with PTS.

Wound Care

Many products are available for the care of venous leg ulcers, including compression wraps, topical antibiotics, ointments, exfoliants, and growth factors. A detailed discussion of these options is beyond the scope of this article. However, two points should be stressed. First, venous leg ulcers are known to frequently recur despite adequate initial therapy, and impose major QOL impairment upon patients.¹⁵ Given the known challenges of obtaining rapid and durable healing of venous leg ulcers, it is critical to obtain such patients the benefit of a wound care clinic that specializes in the efficient delivery of expert ulcer care. Second, the mainstay of venous ulcer care is compression therapy, as noted earlier and as summarized in a recent Cochrane analysis of 39 randomized studies.²⁰ Key principles of venous ulcer management include wound bed preparation using debridement of necrotic tissue, control of wound exudate with foam and alginate primary dressings, and management of bacterial colonization and infection (often guided by quantitative wound cultures). Further detail on ulcer care, along with descriptions of a variety of adjuvant therapies that can be utilized, is available in published guidelines from the American Venous Forum and Society for Vascular Surgery.¹⁵

Endovascular Therapy

Iliac vein obstruction and/or major saphenous venous valvular incompetence are often present in patients with advanced PTS, causing elevations in ambulatory venous pressures, with consequent increase in clinical PTS manifestations. Endovascular implantation of metallic stents can eliminate chronic iliac vein obstruction, which may assist ulcer healing and relieve pain and swelling in PTS patients in noncontrolled studies.^{21–25} For example, the largest series found patients ($n = 464$) with moderate-to-severe PTS to have reduction in pain ($p < 0.0001$ using visual analog scale), severe pain (41–11%), and severe swelling (36–18%); ulcer healing (68%); improvement in QOL; and venous pressure reduction after stent placement.²⁴ Another study showed improvement in limb claudication, outflow fraction, and calf muscle pump function after stent placement.²⁵ Endovenous saphenous vein ablation methods, which have been used by physicians since the late 1990s to manage primary superficial valvular insufficiency, have also been applied to the management of patients with PTS who have an open iliac vein (native, or via stent placement). Preliminary studies suggest that the two methods applied in sequence may offer meaningful clinical improvement to many PTS patients.^{26,27} A variety of open surgical techniques have also been used to provide venous outflow (e.g., venous bypass) or to restore competent deep venous valvular function in PTS patients.¹²

Evidence Gaps in the Management of PTS

The health care environment is changing quickly, driven by advances in science and technology as well as evolving U.S. societal expectations. From a *scientific* perspective, the revolution in genomics has dramatically improved scientists' understanding of our susceptibility to disease and our amenability to specific therapies, raising hopes for the near-future adoption of a targeted, "precision medicine" paradigm. From a *technological* standpoint, dramatic changes in computing, Internet, and mobile technology capabilities have yielded an unprecedented capacity to manage large datasets and to connect people and information. At a *societal* level, questions about the health-economic value proposition of modern medicine (and, in particular, procedure-based medicine) have prompted greater focus on ensuring the real-world effectiveness and patient centeredness of the treatments that are used and paid for. Overall, the expectations of the U.S. public and others who invest in biomedical research are that their dollars will be used to connect more new treatments to more people with greater specificity, rapidity, and impact.

In particular, it is important for interventional radiologists to understand that in a payment system that is focused on rewarding "value" rather than volume, traditional strategies of building procedure volume may not be uniformly supported by hospitals and administrators. Rather, such efforts will need to be matched with initiatives to develop evidence that demonstrates the population effectiveness and cost-effectiveness of new and established treatments, and with efforts to direct their use to those individuals who are most

likely to benefit from them. For venous care, it is easy to see that the writing is already on the wall: (1) insurance companies continue to demand more stringent conditions and documentation for reimbursement of saphenous ablation procedures; (2) in July 2016, the Center for Medicare Services held a MEDCAC panel to evaluate the evidence basis for current treatments for chronic venous disease including PTS; and (3) a large study using the National Inpatient Sample found the additional charges of using thrombolytic therapy for acute DVT to exceed \$57,000 per patient.²⁸

Hence, looking forward, there are several areas of important focus in PTS care. First, while continuing to seek opportunities to help patients who may not be aware of endovascular treatment options, physicians must develop the evidence that enables us to *avoid over-treatment* of patients who do not derive benefit from these therapies. To take one example, consider the use of stents for the obstructed iliac vein. On the one hand, we know that (1) stents can often restore flow in these veins; (2) "iliac vein obstructive lesions" are more frequent than previously recognized in patients with clinical venous manifestations; and (3) new imaging methods such as intravascular ultrasound (IVUS) can help us identify many more of these lesions.²⁹ Together, this would seem to provide a compelling opportunity. However, we must be mindful of a key "home truth": in reality, our basic understanding of which patients are most likely to experience sustained and meaningful benefit is really quite limited. Some patients (especially those with PTS) will experience stent occlusion,²¹ in some cases for potentially addressable reasons (e.g., failure to comply with anticoagulation, or development of new risk factors for clotting), but in other cases for reasons that are not known. We do not know what anticoagulant regimen is most effective in the post-stent PTS patient. Perhaps most troubling, some patients simply do not exhibit a clinical response after stent placement, either due to the presence of underlying deep venous valvular reflux or other factors that are as yet unknown. Although we can identify many iliac vein lesions, we do not have a reliable, noninvasive marker of which iliac vein lesions are physiologically significant, and after stent placement we do not have well-validated parameters that enable us to predict when failure is likely to occur. To direct PTS therapy appropriately, we badly need to know what clinical and imaging features of venous "lesions" actually predict hemodynamic and clinical significance, and a likelihood of durable response with therapy.

Second, it is important for us to continue to evaluate noninvasive methods of PTS treatment. A significant body of literature supports inflammation³⁰ as one element in the pathophysiology of PTS; yet, clinical studies of anti-inflammatory therapies have been limited. Associations have been drawn from large databases between the pathophysiologic elements of arterial and venous diseases.³¹ Could statin therapy play a role in the management of venous disease? In addition, new biological targets for intervention must be developed through careful study of the physiology of thrombus resolution and amplification, endothelial and adventitial responses, and vein wall injury. If nanoparticles can indeed

enable delivery of therapeutic agents to a site of venous thrombosis or endothelial injury, can targeted therapy enable venous healing? And, closer to the present, the potential for structured exercise therapy to help many patients with PTS may be a strong avenue to pursue—might there one day be such a thing as “venous rehabilitation” for PTS patients, as currently exists for patients affected with cardiac conditions?

Finally, there is no question that endovascular therapy has shown strong potential to improve PTS severity and QOL. However, randomized trials comparing endovascular and nonendovascular approaches are badly needed to substantiate the results of preliminary studies while rigorously minimizing the potential for biased assessments. In this respect, physicians who manage PTS can take hope from the strong interdisciplinary collaboration that has occurred around the study of acute DVT therapy during the past decade—two small randomized trials have been published, a larger, U.S.-based, multicenter RCT (the ATTRACT Trial) will be completed later this year, and a rigorous effort is underway to develop a similarly collaborative pivotal clinical trial to evaluate endovascular therapy for the management of advanced PTS.^{32,33}

Conclusion

PTS is a common, morbid, and costly condition. While there is currently no consistently effective treatment for PTS, preliminary studies provide hope that endovascular interventions may produce significant symptom improvement in patients with PTS. However, to achieve these benefits for patients in the value-based future health care environment, interventional radiologists will need to work closely with physician-scientists from other disciplines to more fully develop the evidence around existing PTS therapies. Collaborative interchange among providers with diverse expertise is also most likely to yield novel innovative therapy that benefits PTS patients.

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