

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

Post-thrombotic Syndrome After Deep Venous Thrombosis: Risk Factors, Prevention, and Therapeutic Options

Susan R. Kahn, MD FRCPC MSc
Professor
Department of Medicine
McGill University
Montreal, Canada

H&O What is post-thrombotic syndrome (PTS)?

SK PTS is a syndrome that produces a wide range of symptoms and clinical signs. It is a chronic complication that occurs in approximately 20–40% of patients who have suffered deep vein thrombosis (DVT). Severe PTS occurs in 5–10% of DVT patients. The syndrome can affect young and old patients alike.

PTS represents a constellation of symptoms and signs in the leg which may vary from patient to patient and are not necessarily present in all patients. Symptoms include leg pain, aching, heaviness, swelling, itching, and cramping, particularly when the patient is walking or standing; clinical signs include leg edema, pain when the calf is compressed, varicose veins or telangiectasias (small dilated veins around the ankle), hyperpigmentation of the leg, etc.

PTS can be quite a debilitating condition. Our group has done much research to show that PTS can have a negative impact on the quality of life (QOL).¹ We recruited 387 patients with DVT from 2001 to 2004 at 8 hospitals in Canada. Clinical data were collected at study visits at baseline, 1, 4, 8, 12, and 24 months. We measured generic QOL and venous disease-specific QOL; change in scores over 2 years of follow-up was assessed. We found that among patients who had DVT, those who developed PTS had a much worse QOL than those who did not.

Furthermore, the QOL among those who developed PTS was worse than in patients with other chronic diseases such as chronic respiratory conditions and angina.

H&O How is PTS diagnosed?

SK The syndrome is primarily diagnosed by the presence of typical symptoms and clinical signs in a limb that was affected by DVT. As a wide variety of definitions of PTS have been used by researchers, it has been difficult to compare data across studies. The lack of standardization of PTS may also explain why the difference in incidences reported in various studies is wide-ranging.

A recent paper authored by myself and colleagues² represents an attempt to standardize the definition of PTS that was put forward by the International Society of Thrombosis and Hemostasis (ISTH). The scale that we propose in this paper—and which the ISTH has approved—is the Villalta scale, which we have found to be a reliable and valid instrument to define the presence and severity of PTS in patients with previously confirmed DVT.³

In general, most physicians are not aware of this scale and they base their diagnosis on the presence of typical symptoms: if patients have previously had a DVT and they come back a year later with symptoms, the physician will consider that they have PTS.

Table 1. Villalta's Post-thrombotic Syndrome Scale

Symptoms and Clinical Signs	None	Mild	Moderate	Severe
Symptoms				
Pain	0 points	1 point	2 points	3 points
Cramps	0 points	1 point	2 points	3 points
Heaviness	0 points	1 point	2 points	3 points
Paresthesia	0 points	1 point	2 points	3 points
Pruritus	0 points	1 point	2 points	3 points
Clinical signs				
Pretibial edema	0 points	1 point	2 points	3 points
Skin induration	0 points	1 point	2 points	3 points
Hyperpigmentation	0 points	1 point	2 points	3 points
Redness	0 points	1 point	2 points	3 points
Venous ectasia	0 points	1 point	2 points	3 points
Pain on calf compression	0 points	1 point	2 points	3 points
Venous ulcer	Absent	Present		

Points are summed into a total score (range 0–33). PTS is classified as mild if the Villalta score is 5–9, moderate if the Villalta score is 10–14, and severe if the Villalta score is ≥ 15 or a venous ulcer is present.

Data adapted from Kahn SR et al. *J Thromb Haemost.* 2009;7:879-883.

H&O How does the Villalta scale work?

SK The Villalta scale is a clinical measure for PTS (Table 1); it looks at the severity of 5 patient symptoms and 6 clinical signs, which a clinician (either a nurse or a doctor) has to assess. Basically, a point is given for each of those symptoms and signs (0=no symptom/sign, 1=mild, 2=moderate, 3=severe). A patient is considered to have PTS if he or she has a total added score of 5 or more. The exception is the presence of an ulcer, which is not included as one of the symptoms and signs; the presence of an ulcer, which is known to be a severe manifestation, is an indication of severe PTS, regardless of the total score.

Even though the Villalta scale has been shown to be a good and reliable measure, the average clinician working in the office or hospital may have never heard of it and probably would not know how to use it. For the moment, the scale is being used primarily as a type of research tool. It is not necessarily being used in practice at the present time, although I think it should. It is a good way to follow patients over time and observe changes in their condition.



Figure 1. Compression stockings

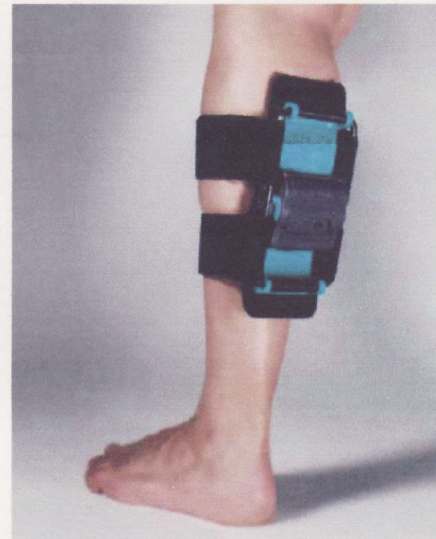


Figure 2. Venowave®

H&O How is PTS treated?

SK Unfortunately, treatment of PTS is limited. We prescribe elastic compression stockings (Figure 1) to patients who have a lot of swelling from PTS; this seems to relieve the symptoms, but currently there is no way to eliminate the manifestation altogether.

Another device that appears to be effective for severe PTS is the Venowave® (Figure 2), which was introduced in a paper by O'Donnell.⁴ He published a small randomized trial about this device—a battery-operated device fastened by a velcro strap around the leg that produces a continuous wave form motion along the calf to help stimulate blood flow back to the heart. Eligible subjects were randomized

to receive Venowave for 8 weeks and a control device for 8 weeks. The 8-week treatment periods were separated by a 4-week wash-out period when no device was used. Clinical success was observed in 10 (31%) participants receiving Venowave and 4 (13%) participants receiving the control device ($P=.11$), with 2 (6%) participants reporting a clinical success with both devices. At least in this small trial, Venowave seemed to be effective in treating severe PTS, but larger studies are necessary.

One drug that has been investigated for its activity in PTS—primarily used in Europe—is horse chestnut extract. It is an herbal remedy taken from the horse chestnut tree, which has a pharmacologic component (aescin) that seems to have effect in some patients. We sometimes prescribe it to patients who do not have success with the stockings. In my experience, it generally does not have adverse side effects.

An ulcer of the leg will require compression and dermatologic treatment, but there are no surgical procedures that have been shown to be effective for PTS.

Another study that we have just completed but have not yet analyzed is the EXPO trial, which is a randomized trial that evaluated whether exercise training given for 6 months in patients with PTS might improve their condition. Exercise training has been shown to be effective in patients who have chronic arterial blockages, and therefore we hypothesized that the same may apply for patients with chronic venous blockages or insufficiency, as is seen in PTS. We are going to be analyzing the data in the coming months.

H&O Are there known predictors of PTS?

SK In the Venous Thrombosis Outcome (VETO) study,⁵ which was a prospective cohort study conducted at 8 centers in Canada, 387 patients who had DVT were recruited. We followed them for 2 years and obtained clinical information, applying the Villalta scale to check the severity of PTS. We found in that study that, overall, 43% of patients developed PTS—approximately 30% had mild, 10% had moderate, and 3% had severe cases. In addition to looking at the incidence of PTS, we also tried to determine what factors predicted the development of PTS; it would be ideal if a physician can look at a patient in the office and determine the likelihood of PTS development in that individual. We found that there were certain factors that predicted the development of PTS, the strongest predictor being the presence of DVT symptoms and clinical signs at 1 month after treatment of DVT. In other words, if a patient's leg had not

improved by 1 month, that was a very strong predictor of developing PTS within the next 2 years. We also found that people who had higher body mass index, those who had previous DVT in the same leg, and those who were older had a higher risk. Additionally, we found that the more extensive the patient's initial DVT was, the higher the chance of developing PTS (ie, the bigger the clot is in the patient's vein, the more likely it is to cause permanent damage leading to PTS).

H&O Are there any preventative measures that clinicians can take?

SK Unfortunately, there are not many options to treat PTS. However, there are a couple of points that are important to emphasize in terms of prevention. First of all, because we and other investigators have shown that a repeated DVT in the same leg increases the risk of developing PTS, it is very important for patients who have had a DVT to receive an adequate duration of anticoagulation therapy to prevent subsequent DVT. Secondly, there have been a couple of small studies conducted at single centers that show that the daily use of elastic compression stockings after DVT can substantially reduce the risk of PTS.^{6,7}

My colleagues and I are in the process of completing recruitment for a large, first North American, randomized, multicentered trial—it will be the first to compare compression stockings to placebo stockings—to assess whether compression stockings are as effective at preventing PTS as was shown in the 2 smaller studies.

Another avenue of research involves evaluating whether weight loss can reduce the risk of PTS.

References

1. Kahn SR, Shbaklo H, Lamping DL, et al. Determinants of health-related quality of life during the 2 years following deep vein thrombosis. *J Thromb Haemost.* 2008;6:1105-1112.
2. Kahn SR, Partsch H, Vedantham S, et al. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. *J Thromb Haemost.* 2009;7:879-883.
3. Kahn SR. Measurement properties of the Villalta scale to define and classify the severity of the post-thrombotic syndrome. *J Thromb Haemost.* 2009;7:884-888.
4. O'Donnell MJ, McRae S, Kahn SR, et al. Evaluation of a venous-return assist device to treat severe post-thrombotic syndrome (VENOPTS). A randomized controlled trial. *Thromb Haemost.* 2008;99:623-629.
5. Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med.* 2008;149:698-707.
6. Brandjes DP, Büller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet.* 1997;349:759-762.
7. Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med.* 2004;14:249-56.