

Post thrombotic syndrome: prevention, management and clinical biomarkers (state of the art)

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Abstract

The post-thrombotic syndrome (PTS) develops in up to one half of patients after symptomatic deep venous thrombosis (DVT) and is the most common complication of DVT. Typical features of PTS include chronic pain, swelling, heaviness, oedema and skin changes in the affected limb. In severe cases, venous ulcers may develop. Preventing ipsilateral recurrence of DVT, by ensuring an adequate duration and intensity of anticoagulation for the initial DVT and by prescribing situational thromboprophylaxis after discontinuation of oral anticoagulants, is likely to reduce the risk of developing PTS. Pending the results of ongoing studies, stockings are recommended in patients with persistent symptoms or swelling after DVT. Future research should focus on elucidating the pathophysiology and risk factors for PTS, assessing the safety and effectiveness of catheter-directed thrombolysis to prevent

PTS and evaluating the optimal use of compression stockings to prevent and treat PTS. In addition, new therapies to treat PTS should be sought and evaluated.

Introduction

The postthrombotic syndrome occurs frequently after DVT. Patients with extensive DVT and those with more severe postthrombotic manifestations 1 month after DVT have poorer long-term outcomes.

The present review focuses on risk factors for PTS after DVT and the available means to prevent and treat PTS, highlighting new information and concepts in the field. In addition, gaps in our understanding of PTS that merit further research are noted. Readers are also encouraged to consult a recently published scientific statement and clinical guidance

document that focus on PTS¹. Complication after episode of DVT prevalently due by venous hypertension which results from valvular incompetence, outflow obstruction, calf muscle dysfunction.

To the best of our knowledge, few studies in the United States¹¹

have attempted to determine the costs associated with the entire range of long-term complications of DVT.

The costs of DVT have been studied in two US retrospective observational studies that used claims databases. Spyropoulos et al. identified hospital claims containing DVT or PE as the primary or secondary diagnosis from 1998 to 2004⁶¹. Average per-patient costs were estimated at US\$7712 for the initial hospitalization and US\$2101 per year for patients readmitted to hospital during follow-up. Higher rates of hospital readmissions during follow-up (24.9% vs. 7.0%) and longer duration of initial parenteral therapy (13.0 vs. 7.4 days) were reported than in our study. Although the clinical manifestations of PTS are well known, the quality-of-life and socioeconomic impacts of PTS have not been extensively documented, except

for the most severe forms of the syndrome, such as venous leg ulcer^{12,13}.

PTS is burdensome and costly to patients and society. At present, effective, evidence-based treatments for PTS are lacking, which is a source of difficulty and frustration for patients with PTS. Until effective treatments are found, prevention of PTS is the key to reducing its overall impact on patients and society. Preventing DVT recurrence is likely to reduce the risk and costs of PTS. Daily use of graduated ECS after DVT may reduce the risk of PTS. As of yet, there is no established role for thrombolysis in preventing PTS^{14,15}.

The present review aims to analyze the large amount of informations on this issue trying to find some conclusions on a topic that is often unclear and confused.

Underlying pathophysiology of PTS

PTS is a direct consequence of DVT as a result of venous hypertension (ie, increased venous pressures). Venous hypertension reduces calf muscle perfusion, increases tissue permeability, and promotes the associated clinical manifestations of PTS. Two pathologic mechanisms contribute to venous

hypertension: persistent (acute, then residual) venous obstruction and valvular reflux caused by damage to vein valves¹⁷. Standard anticoagulant treatment of DVT prevents thrombus extension and embolization to the pulmonary arteries but does not directly lyse the acute thrombus, and in many cases only partial clearance of thrombus occurs. Inflammation may play a role in promoting the development of PTS by delaying thrombus resolution and by inducing vein wall fibrosis, which promotes valvular reflux.^{18,19}

The apparent lack of decrease in VTE incidence over time could be the result of more complete case ascertainment in recent compared to older studies, but might also be due to aging of the population, exposure to more or new risk factors, and persistent under-utilization of appropriate thromboprophylaxis. There are approximately 200,000–250,000 new cases of VTE in the US per year²⁰. Thus, it is convincing that VTE represent a major global health problem.

Incidence for PTS after DVT

Population-based studies demonstrate that reliable estimates of the incidence and prevalence of PTS are difficult to obtain.

PTS is a frequent complication of DVT. It develops in 20% to 50% of patients within 2 years of DVT diagnosis and is severe in 5% to 10% of cases⁶⁰. Hence on average, about 6 of 10 patients can expect to recover from DVT without any residual symptoms, 3 of 10 will have some degree of PTS, and 1 in 10 to 1 in 20 will have severe PTS, which can include leg ulcers.²⁰

Preventing first and recurrent DVT

Preventing the first occurrence of DVT by improving the systematic use of thromboprophylaxis in high-risk hospitalized patients as recommended in evidence-based consensus guidelines will prevent some cases of PTS²⁵⁻²⁷. Because ipsilateral DVT recurrence is a strong risk factor for PTS, reducing the risk of recurrent DVT by providing optimal anticoagulation of appropriate intensity and duration to treat the initial DVT is an important clinical goal²⁸. In patients treated with vitamin K antagonists, frequent, regular INR monitoring to avoid subtherapeutic INRs in the first months after DVT may also reduce the risk of PTS^{29,30}. Data are insufficient to make specific recommendations regarding

choice of anticoagulant to treat DVT, namely a vitamin K antagonist vs a direct, target-specific oral anticoagulant vs LMWH monotherapy, on the outcome of developing PTS²¹.

Methods

To perform a systematic review of clinical studies that have examined the incidence, clinical features, risk factors and management of post-thrombotic syndrome.

Using combinations of keywords venous thrombosis, postphlebotic syndrome, thrombophlebitis, biomarkers, post-thrombotic syndrome, the MEDLINE database was searched for English language articles published. Retrieval and review of articles were restricted to clinical studies in humans that described long-term outcomes after objectively confirmed PTS.

Diagnosis of PTS

At baseline visit the physician examined the patient's legs and classified the clinical categories and severity of PTS using the different scoring systems.

Three clinical scales for the diagnosis of PTS have been developed²⁹⁻³¹ and are summarised in Table 2. These have been used to assess the presence and grade the severity of PTS in a number of clinical studies, including trials of therapies to prevent or treat PTS.

However, none has undergone full evaluation of reliability, validity or responsiveness to change and their use for the routine clinical monitoring of DVT patients has not been assessed. Moreover, differences in the test characteristics of these measures could help to explain the differing rates of PTS that have been reported in long-term follow-up studies of patients with DVT.

The best known is the CEAP (Clinical, Etiologic, Anatomic, Pathophysiologic) classification, which categorises patients into one of seven classes based on clinical signs, with modifiers that reflect the underlying cause (congenital, primary, or secondary to DVT), anatomic distribution (superficial, deep, or perforating veins), and pathophysiologic condition (reflux, obstruction, or both).^{30,32}

Risk factors for PTS

Although it is not yet possible to precisely predict the absolute risk of PTS in an individual patient with DVT, research done over the last 5 to 10 years has provided new information on various risk factors for PTS, which has been detailed in 2 recent reviews.^{19,20} This information is summarized next, grouped according to the time points at which patients with DVT are assessed in clinical practice.

Risk factors apparent at time of DVT diagnosis.

- DVT location: Risk of PTS is higher (two- to threefold) after proximal (especially with involvement of the iliac or common femoral vein) than distal (calf) DVT.
- Previous ipsilateral DVT.
- Preexisting primary venous insufficiency: up to twofold increased risk of PTS.
- Elevated body mass index (BMI): obesity (BMI >30) more than doubles the risk of PTS.
- Older age increases the risk of PTS; reported increased risk from 30% to threefold.

The following factors appear to have little or no effect on the risk of developing PTS: sex, whether DVT was provoked vs unprovoked, and biological thrombophilia.

Risk factors related to treatment of acute DVT.

- Quality of oral anticoagulation: PTS risk increases twofold if the level of anticoagulation is inadequate (eg, subtherapeutic international normalized ratio [INR] >50% time) during the first 3 months of treatment with vitamin K antagonists.
- Choice of anticoagulant to treat DVT: It is not known whether use of the new direct oral anticoagulants to treat DVT influences the risk of PTS, compared with treatment with low-molecular-weight heparin (LMWH) or vitamin K antagonists. A meta-analysis of available data suggested that use of LMWH monotherapy to treat DVT may lead to lower rates of PTS than treatment with LMWH for 5 to 7 days followed by vitamin K antagonists.²¹

Large multicenter trials that use validated criteria to diagnose PTS are needed to confirm the effectiveness of extended LMWH in patients at high risk for PTS, and also to assess the effectiveness of new direct oral anticoagulants in preventing PTS.

- The potential role of thrombolysis in reducing the risk of PTS is discussed in the next section.

Risk factors apparent during follow-up after DVT.

- Ipsilateral DVT recurrence: Increases risk of PTS four- to sixfold, presumably by damaging compromised venous valves or aggravating venous outflow obstruction.
- Persistent venous symptoms and signs 1 month after acute DVT: Increases risk of subsequent PTS.^{22,23}
- Residual thrombosis on ultrasound (eg, 3-6 months after acute DVT): Modest (1.5- to twofold) increased risk of PTS.
- Persistent elevation of d-dimer: Elevated levels of d-dimer in the weeks to months after DVT may be a modest risk factor for PTS.²⁴

Prevention of PTS

Additional common sense lifestyle advice that is relevant to all patients with chronic venous insufficiency includes reducing venous stasis by keeping active and avoiding a sedentary lifestyle; raising the legs on a footrest when seated or elevating the legs on a firm pillow when lying down; avoiding prolonged exposure to heat, which can aggravate symptoms of leg heaviness and swelling; maintaining a healthy, nonobese body weight; and using a moisturizing lotion to avoid skin dryness and breakdown. Thromboprophylaxis is an effective means of preventing DVT, it is highly likely, by extrapolation, that use of thromboprophylaxis in high risk patients and settings as recommended in evidence-based consensus guidelines⁴⁷ will prevent cases of PTS. Further, while thromboprophylaxis is effective, its use does not eliminate the risk of VTE. Moreover, nearly 50% of VTE events occur unpredictably and are therefore not preventable with thromboprophylaxis¹⁴.

Catheter-directed thrombolysis, which involves direct delivery of a fibrinolytic drug into the clot via a catheter introduced within the thrombosed vein, may be safer and more effective than systemic

Thrombolytic therapy and could hold promise as a means of preventing PTS⁵⁰.

Elastic compression stockings

Elastic compression stockings (ECS), by reducing leg swelling and venous hypertension, could plausibly play a role in preventing PTS. However, there are conflicting data on the long-term effectiveness of ECS to prevent PTS.⁴⁹

Prandoni⁵⁹ showed in a trial of a total of 267 patients with the first episode of proximal deep venous thrombosis were randomized to wear either thigh-length or below-knee ECS for 2 years. After 3, 6, 12, 18, 24, and 36 months, they were assessed for PTS manifestations according to the Villalta scale. PTS developed in 44 (32.6%) of the 135 patients randomized to thigh-length ECS and in 47 (35.6%) of the 132 allocated to below-knee ECS, for an adjusted hazard ratio of 0.93 (95% confidence interval, 0.62-1.41). Severe PTS developed in 3 patients in each group. ECS-related side effects developed in 55 (40.7%) of the 135 patients allocated to thigh-length ECS and in 36 (27.3%) of those randomized to the below-knee group (P = .017), and led to premature discontinuation of their use in 29 (21.5%)

and 18 (13.6%) patients, respectively. He conclude that thigh-length ECS do not offer a better protection against PTS than below-knee ECS and are less well tolerated.

Treatment of PTS

Clinicians often prescribe physical compression methods to counteract increased venous pressure. ECS on an as-needed basis may reduce swelling in some patients with PTS⁵⁴ and should be tried. However, their treatment benefit has not been definitively shown in the setting of PTS and is primarily extrapolated from studies of patients with chronic venous disease⁵⁵. Although a considerable number of patients wearing below-knee CES still develop PTS, the rate of severe sequelae is acceptably low. Whether aggressive treatment of the initial thrombosis can further decrease PTS rate remains to be demonstrated, as does the assessment of the optimal duration of CES for its prevention⁵⁹.

The recommendations about the duration and type of long term treatment in patients with a first episode of VTE are unmarized in. Although VKA is mostly used for longterm treatment, LMWH is preferred in

patients with cancer⁵⁷. The endovenous 980-nm diode laser surgery is a safe and effective, cosmetically preferential procedure while a long-term follow-up is being awaited⁵⁸.

Conclusion

PTS leads to chronic and severe morbidity. It's best treatment remains prevention and early identification of risk factors, prevention of DVT, and aggressive management of DVT. In established DVT patients, anticoagulation, compression, exercise, and skin care measures are needed in order to prevent DVT recurrence and long-term sequelae such as PTS. Post-thrombotic syndrome is burdensome and costly to patients and society.

Until effective treatments are found, prevention of PTS is the key to reducing its overall impact on patients and society.

Most physicians believe that ECS are useful for preventing PTS and for managing venous symptoms, many do not routinely prescribe them, and there is considerable variation in practice regarding the timing of initiation of ECS, duration of therapy, and compression

strength. On the other hand, DVT patients appear to be willing to purchase

ECS despite their cost, tolerate them well, and most are willing to wear them daily. As of yet, there is no established role for thrombolysis in preventing PTS. With evaluation of new anticoagulants there is no doubt that in the near future the treatment of patients with VTE will become more patient friendly, effective, safe and evidence based.

In terms of PTS prevention, anticoagulation with good medication adherence is the most important tool. If a VKA is chosen, careful INR monitoring is critical. LMWH have anti-inflammatory properties, and may be superior to VKA, whereas the effectiveness of DOACs in this setting is uncertain. The efficacy of ECS for prevention of PTS remains equivocal and ECS should be prescribed for acute symptoms, CVI, and depending on clinician and patient preference. Locoregional interventional therapies likely reduce acute DVT symptoms and long-term (5 year) PTS risk, but only for high-risk patients (e.g., those with extensive proximal DVT). After PTS is established, ECS are the mainstay of treatment. Venoactive medications and interventional approaches require

additional evaluation before they can be recommended.

The management of acute DVT and chronic PTS remains complex, with many possible avenues of improvement.

At present, outcome assessment for patients with DVT is performed in a cross-sectional manner, with use of validated measures applied just a few times during patient follow-up. However, PTS is an ongoing malady that affects patients every day.

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Key Words: Deep venous thrombosis, Upper extremity, Post-thrombotic syndrome, Biomarkers, Review