Thrombosis Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Prevention and treatment of the post-thrombotic syndrome

Oleg Pikovsky [a], Anat Rabinovich [b,*]

[a] Blood Bank and Pheresis Unit, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Be'er Sheva, Israel
[b] Thrombosis and Hemostasis Unit, Hematology Institute, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Be'er Sheva, Israel

ARTICLE INFO

Article history:
Received 30 March 2017
Received in revised form 19 June 2017
Accepted 10 July 2017
Available online xxxx

Keywords:
Post-thrombotic syndrome
Deep vein thrombosis
Anticoagulation
Compression stocking
Catheter-directed thrombolysis
Rutosides
Defibrotide
Hidrosmin

ABSTRACT

Post-thrombotic syndrome (PTS) is a complication that develops in up to 50% of patients with deep vein thrombosis (DVT) and manifests as symptoms and signs of chronic venous insufficiency of varying severity. PTS negatively affects patient's quality of life and causes significant burden to the healthcare system. The risk for PTS development can be markedly reduced by preventing DVT and providing appropriate anticoagulation once it develops. Patients with extensive proximal (iliofemoral) DVT may benefit from invasive interventions, such as catheter-directed thrombolysis. The effectiveness of elastic compression stockings (ECS) for PTS prevention has not been conclusively demonstrated in randomized trials.

Treatment of PTS is primarily based on ECS, exercise and lifestyle modifications. The effectiveness of various pharmacologic agents for PTS treatment remains controversial. Surgical or radiological interventions for vein reconstruction or revascularization may be considered in refractory cases.

This review summarizes current evidence regarding prevention and treatment of PTS of the lower limbs in adults.

Contents

1. Introduction

Post-thrombotic syndrome (PTS) is a common chronic complication of deep-vein thrombosis (DVT), which develops in 20 to 50% of DVT patients. Anticoagulation alone is usually insufficient to eliminate the risk of PTS [1–3]. The majority of patients will develop a mild to moderate

* Corresponding author at: Thrombosis and Hemostasis Unit, Hematology Institute, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, POB 151, Be'er-Sheva 84101, Israel.
E-mail address: anatra@clalit.org.il (A. Rabinovich).

http://dx.doi.org/10.1016/j.thromres.2017.07.008
0049-3848/

form of PTS, characterized by a sense of heaviness, fatigue and minor swelling of the affected leg, typically in the evening. Five to ten percent of patients develop a severe form of PTS [4], manifested by severe pain, intractable edema and chronic ulceration. These patients typically require intensive medical attention [5,6]. The pathogenesis of PTS is complex and not fully elucidated. Two major pathogenic factors are thrombotic outflow obstruction [7–10] and valve incompetence (reflux) [11–14], both lead to venous hypertension and subsequent PTS development. PTS can considerably impair patient's quality of life (QOL) [15] and cause significant burden to the healthcare system [16–18]. PTS is also considered as a risk factor for recurrent DVT and increases its risk up to threefold [19].

The principal objective of this review is to provide healthcare professionals involved in the care of DVT patients with practical tools that may improve prevention and management of adult patients with PTS of the lower limb.

2. Prevention of PTS

2.1. Prevention of DVT

Since PTS is a complication of DVT, prevention of DVT in patients at risk, and decreasing the risk of recurrent DVT after the first event, appears to be the single most important intervention to prevent PTS. The importance of maximizing the efficacy of primary or secondary DVT prophylaxis in high-risk settings is emphasized in various reports and guidelines [20–23].

2.2. Efficacy of anticoagulation

Insufficient anticoagulation with vitamin K antagonists (VKA) during the first three months of DVT treatment increases the risk of PTS, as reported in two studies [24,25]. In the first study, patients with International Normalized Ratio (INR) values lower than 2.0 > 50% of the treatment period had an elevated risk for PTS (odds ratio (OR) 2.71 [95% confidence interval (CI) 1.44–5.10]). The second study demonstrated an OR of 1.84 (95% CI 1.13–3.01) for PTS in patients with INR below 2.0 for 20% or more of the first three months of therapy. Therefore, rigorous INR monitoring is recommended, particularly during the first three months of treatment, in order to diminish the risk of PTS [26]. Nevertheless, even the best anti-thrombotic treatment will not completely eliminate the risk of PTS, and this complication still develops in patients under optimal anticoagulation.

2.3. Type of anticoagulant

It has been suggested that low molecular weight heparins (LMWH) are more effective than VKA for PTS prevention. This effect was partially attributed to the anti-inflammatory properties of the LMWHs [27]. A pooled analysis of two studies [28] demonstrated a risk reduction of 87% in the incidence of venous ulcers with LMWH compared to standard VKA treatment (95% CI 0.02–0.71). A pooled analysis of five studies demonstrated a relative risk (RR) of 0.66 (95% CI 0.57–0.77) for complete recanalization of the affected veins with LMWH compared to VKA [28]. One study reported an OR of 0.77 (95% CI 0.67–0.90) favoring LMWH vs VKA for the presence of 8 patient-reported post-thrombotic syndrome signs and symptoms [29]. However, studies included in these reports had several serious limitations, for example: none of them planned to assess PTS risk reduction as a primary outcome [29–33]; one study [29] used patient self-reports for PTS diagnosis rather than a validated PTS score, raising a question regarding accuracy of PTS diagnosis [34], while others [30–33] used various measurements of venous flow as their outcome rather than clinical PTS. Also, PTS development was assessed three months after DVT in four studies [29–31,33] which might be too early for full expression of PTS symptoms and signs (according to guidelines [23] the diagnosis of PTS should not be made earlier than 6 months post DVT). Considering these limitations, findings favoring LMWH over VKA for PTS prevention should be interpreted with caution, especially in light of results from other reports that did not find a statistically significant benefit of LMWH over VKA for PTS risk reduction [35,36]. To date, the use of LMWH monotherapy for PTS prevention in patients after DVT remains controversial and cannot be routinely recommended.

Whether treatment of DVT with direct oral anticoagulants (DOACs) is more effective than VKA in preventing PTS is still an unanswered question [37]. It seems plausible that superior anticoagulation control and patient compliance attributable to DOACs may reduce PTS risk, but this notion has yet to be confirmed. A post-hoc analysis of the Einstein study failed to demonstrate a statistically significant reduction in the risk for PTS in the rivaroxaban treatment group versus LMWH/VKA [38]. Well-designed randomized controlled trials are required to assess the effect of treatment with DOACs on the risk of PTS.

The role of statins as an adjunct to anticoagulation in the prevention of recurrent DVT and PTS is still unclear and further studies are needed. One study of combined treatment with rosuvastatin and LMWH versus LMWH therapy alone reported reduction in PTS incidence (Villalta score > 5; 38.3% vs. 48.5%, $p = 0.019$) after three months of treatment [39]. The major limitation of this study was a short (three months) period of therapy and follow up.

2.4. Elastic compression stockings (ECS) (Table 1)

Wearing of ECS has been considered for decades as an effective measure for PTS prevention. However, this assumption has not been based on good quality data. Two randomized open-label trials [40,41] demonstrated that wearing knee-high 30–40 mm Hg ECS for more than two years after proximal DVT can reduce the risk for PTS. In the first study, the hazard ratio for PTS in the ECS group versus control was 0.49 (95% CI 0.29–0.84); in the second trial, mild-to-moderate PTS was reported in 20% of the 96 patients in the stocking group, and in 47% of the 98 patients in the control group ($p < 0.001$). Of note, neither of the above studies was placebo controlled. In contrast, a large multicenter placebo-controlled trial in 803 patients (SOX Trial) found neither a benefit of compression stockings during two years for PTS prevention nor a decrease in the rate of recurrent DVT or improvement of QOL [42]. The lack of benefit of compression stockings for PTS prevention was also demonstrated in a recent meta-analysis of 6 randomized controlled trials, comparing ECS with no stockings [40,41,43,44] or placebo [42,45] (OR 0.56 [95% CI 0.27–1.16]) [46]. However, studies included in this meta-analysis were clinically heterogeneous: as noted, two studies [42,45] were double blinded and placebo controlled and the others [40,41,43,44] compared ECS to no intervention; two studies used PTS diagnostic scores other than the Villalta/modified Villalta score [43,45]; time of initiation of ECS therapy after DVT ranged from two days [44] to one year [45]; different pressure class stockings were used across the studies, while the effect of stocking pressure on PTS risk is a point of controversy [47,48]. Accordingly, authors conclude that the results of this review should be interpreted with caution.

A recent report of the OCTAVIA study [49], a multicenter single blinded non-inferiority randomized trial that compared PTS risk after 12-month or 24-month period of ECS use, found that the incidence of PTS was 19.9% (95% CI 16% - 24%) in the 12-months arm and 13.0% (9.9%–17%) in the 24-months arm, for an absolute difference of 6.9% (95% CI upper limit 12.3%), demonstrating that a 12-month period of ECS use was not non-inferior to 24 months in decreasing PTS risk. Accordingly, longer period of ECS use after DVT may still have a role in PTS prevention.

Two randomized trials aimed to evaluate the effect of ECS on PTS risk are currently under way. The CELEST trial (NCT01578122) is a controlled, randomized, multicenter, non-inferiority double-blind trial designed to demonstrate non-inferiority of ECS with ankle pressure 25 mm Hg versus 35 mm Hg on the risk of PTS. The IDEAL DVT study

Please cite this article as: O. Pikovsky, A. Rabinovich, Prevention and treatment of the post-thrombotic syndrome, Thromb Res (2017), http://dx.doi.org/10.1016/j.thromres.2017.07.008