REVIEW ARTICLE

The Treatment of Post-Thrombotic Syndrome

The Role of Endovascular Recanalization in Chronic Iliac Vein Obstruction

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SUMMARY

Background: Post-thrombotic syndrome (PTS) arises in 20–50% of patients who have sustained a deep vein thrombosis and markedly impairs their quality of life.

Methods: This review is based on pertinent publications retrieved by a selective literature search in PubMed and the Cochrane Library, and on the guidelines of the German Societies of Phlebology and Vascular Surgery (*Deutsche Gesellschaft für Phlebologie, Deutsche Gesellschaft für Gefäßchirurgie*).

Results: The treatment options are conservative treatment with compression and patient exercises, endovascular recanalization with stent angioplasty, and open bypass surgery of the iliac obstructions. The endovascular techniques yield patency rates of 73 to 100%, with thrombotic stent occlusion and hematoma as potential complications. The open operations have only been documented in studies with small case numbers (3 to 85 cases per study, patency rates 58 to 100%). The complications of these invasive procedures can include thrombotic bypass occlusion, hematoma, and wound infection. There have been randomized trials of conservative treatment, but not of surgical treatment. The American Heart Association, in its guidelines, gives the same weak recommendation for all surgical methods (IIb).

Conclusion: All conservative options should be exhausted as the first line of treatment. If PTS symptoms persist and markedly impair the patient's quality of life, the possible indication for surgery should be considered. As PTS hardly ever leads to death or limb loss, its treatment should be as uninvase as possible. Endovascular recanalization is an attractive option in this respect. A conclusive evaluation of the role of endovascular procedures in PTS must await randomized trials of this form of treatment and of the optimal stent configuration.

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In about 20% to 50% of patients in whom a deep vein thrombosis has been diagnosed, a postthrombotic syndrome follows. This remains the case even when appropriate anticoagulation treatment has been given (1, 2).

In the pathogenesis of postthrombotic syndrome, venous hypertension plays a central role. Incomplete spontaneous recanalization leads to chronic venous obstruction. Venous wall fibrosis and damaged venous valves cause reflux. All this leads to venous hypertension. Venous hypertension in turn causes dilatation of the capillaries and increased endothelial permeability to plasma, proteins, and erythrocytes. Consequences include edema, inflammation, hyperpigmentation of the skin, and eczema or even the development of a venous ulcer. In addition to all of this, venous hypertension causes distension of the deep veins with an increase in valvular incompetence, which is then transmitted to the superficial venous system via the perforating veins (secondary varicosis) (3, e1–e3).

Typical symptoms are: heaviness and tension, itching, cramp, and pain. Venous claudication occurs in the form of a bursting pain during walking, which eases during standing or when the affected leg is raised up (e1).

Clinical signs include phlebedema, venous ectasia, collateralization, stasis dermatitis, hyperpigmentation, atrophie blanche, dermatolipofasciosclerosis, and venous ulcer. Dermatolipofasciosclerosis leads to restriction of movement in the ankle (arthrogenic stasis syndrome). Because of this, the calf muscle pump ceases to be sufficiently activated, thus further reinforcing the vicious circle of venous hypertension (4, e1) (*Figure 1*).

Postthrombotic syndrome greatly impairs patients' quality of life and has considerable socioeconomic consequences. In the USA, the average yearly costs for these patients are estimated at about USD 20 500 per patient (1, 5).

Postthrombotic syndrome is diagnosed on the basis of the symptoms and signs mentioned above. Special scoring systems have been developed (e.g., Villalta, Ginsberg, and Brandjes scores), which assign point scores to the symptoms and signs according to their severity (6–8, e3). The primary diagnostic imaging technique used is duplex ultrasonography. If iliac/caval

Figure 1:
Clinical signs of postthrombotic syndrome

a) venous leg ulcer
b) venous collaterals

obstructions are suspected, computed tomographic (CT) or magnetic resonance (MR) venography aids further clarification. Gadolinium-enhanced MR-venography is particularly well suited to reliable detection of intraluminal trabeculae and vascular wall thickening (9).

The location and extent of the initial deep vein thrombosis are the most important predictors of the occurrence of postthrombotic syndrome (2, e4–e7). For example, deep vein thrombosis of the iliac veins or of the common femoral vein (CFV) carries a significantly higher risk of postthrombotic syndrome than a popliteal or crural deep vein thrombosis (risk ratio 2.3; 95% confidence interval [95% CI]: [1.0; 5.6] (10). Where the deep vein thrombosis occurs in iliac veins, 2 years later residual thrombi are present in 33% of cases, whereas thrombi in distal venous segments have resolved more completely (3% residual thrombi after 2 years) (10). In one study, Kahn et al. showed that iliac location of a deep vein thrombosis was the strongest risk factor for the development of severe postthrombotic syndrome (11). Other risk factors include:

- Advanced age
- Obesity
- Subtherapeutic INR values during treatment for deep vein thrombosis (1, 2, 12, e4).

The aim of this article is to provide an up-to-date overview of treatment for postthrombotic syndrome, with a particular emphasis on the role of endovascular recanalization. Prevention of postthrombotic syndrome is not covered in this article.

Methods

This review is based on a selective literature search of the PubMed database, the Cochrane Library, and the guidelines of the German Society of Phlebology (Deutsche Gesellschaft für Phlebologie) and the German Society of Vascular Surgery (Deutsche Gesellschaft für Gefäßchirurgie). The search terms used were “postthrombotic syndrome,” “post-thrombotic

syndrome,” and “postthrombotisches Syndrom.” From the search results, we selected those publications relating to the treatment of postthrombotic syndrome. Case reports, (animal) experimental studies, and articles on postthrombotic syndrome of the upper extremity or in children were excluded.

Conservative treatment of postthrombotic syndrome

The goal of treatment for postthrombotic syndrome is symptomatic relief, since the condition itself is not curable. Compression therapy is used, the effects of which include the following:

- Reducing the diameter of the vein and hence improving venous valvular function,
- Accelerating venous backflow, and
- Preventing and reducing leg edema (6, 13, 14).

Only two small randomized studies have been published on the treatment of postthrombotic syndrome with medical compression stockings (n = 115 patients). These studies did not show any advantage from the wearing of compression stockings (7, 15)—a finding, however, that does not accord with clinical experience.

Although the Cochrane Review of 2003, which included the study by Ginsberg et al., does not recommend compression stockings to treat postthrombotic syndrome (7, 16), the American Heart Association (AHA) supports a weak recommendation because of their low side effects (allergic skin reaction) and possible utility (especially, edema reduction), so long as any contraindications have been excluded (e.g., advanced peripheral arterial occlusive disease, decompensated heart failure) (recommendation class IIb, evidence level C (17). According to the current guidelines of the German Society of Phlebology (DGP), compression stockings improve subjective venous symptoms; especially, leg edema is reduced (evidence level A) (13). In their most recent publication on the treatment of postthrombotic syndrome, Kahn et al., whose SOX study showed no advantage of compression stockings in preventing postthrombotic

Figure 2: Femoral crossover bypass as described by Palma and Esperon

syndrome, recommend the wearing of knee-high compression stockings (20 to 30 mmHg), and that the compression pressure can be increased up to 40 to 50 mmHg if needed (1, 18).

The evidence in the literature for the use of compression stockings in treatment of venous ulcer is clearer. Seven studies have shown that chronic venous ulcers heal more quickly with compression than with wound care without compression. Compression stockings are therefore recommended both in the DGP guidelines and those of the AHA (recommendation class I, evidence level A) (13, 17, 19).

According to the DGP guidelines, intermittent pneumatic compression improves the symptoms of severe postthrombotic syndrome (evidence level B) (14). In their recent study, Kahn et al. also recommend intermittent pneumatic compression in patients with moderate to severe postthrombotic syndrome (1).

Because of the lack of evidence of positive effect, and also the possibility of long-term side effects, medical therapy with venoactive drugs (e.g., rutoside) is not recommended (1, 20).

Exercise training and physiotherapy aim to improve symptoms, mainly by improving the calf muscle pump function. Two studies have investigated the efficacy of this treatment in comparison with a control group that

did not exercise. The exercise group showed improvement of symptoms and quality of life, leg strength, and mobility (21, e8). For this reason the AHA recommends a supervised exercise program (recommendation class IIa, evidence level B) (17).

Surgical treatment of postthrombotic syndrome

There are no randomized controlled studies of surgical treatment, either in the form of comparison of operative versus conservative treatment or of randomized comparisons between the various surgical treatments. In terms of open and hybrid operations, only small, nonrandomized studies with low patient numbers and variable follow-up have been carried out (evidence level C). With regard to endovascular operations, at least studies with larger patient numbers do exist (Neglén et al., n = 982), meaning that evidence level B is attained (22).

In patients with severe postthrombotic syndrome, the iliac obstructions should be treated first. Interventions to correct reflux can only succeed if ilio caval outflow is restored (17, 23, e9).

Open surgical treatment of obstruction/occlusion

In patients with unilateral iliac vein obstruction, Palma and Esperon described a femorofemoral crossover

TABLE

Studies of open surgical treatment of postthrombotic syndrome

Authors (reference)	Year	Number of extremities	Follow-up (months)	Patency rate (%)	Improvement of symptoms (%)	Transplant material	Operation
Palma and Esperon (24)	1960	8	Up to 36	n.a.	88	Vein	Femorofemoral crossover bypass
May (e11)	1981	66	n.a.	73	n.a.	Vein	
Husni (e12)	1983	85	6–180	70	74	Vein (n = 83) PTFE (n = 2)	
Halliday et al. (e13)	1985	47	Up to 216	75	89	Vein	
AbuRahma et al. (e14)	1991	24	66	75	63	Vein	
Gruss und Hiemer (e10)	1997	19 32	n.a. n.a.	71 85	82	Vein PTFE	
Garg et al. (25)	2011	29	60	70	n.a.	Vein (n = 25) PTFE (n = 4)	
Husfeldt (e15)	1981	4	4–30	100	100	PTFE	Femorocaval or ilio-caval bypass
Dale et al. (e16)	1984	3	1–30	100	100	PTFE	
Gloviczki et al. (e17)	1992	12	1–60	58	67	PTFE: 11 Dacron:1	
Alimi et al. (e18)	1997	8	19.5 (mean)	88	88	PTFE	
Garg et al. (25)	2011	17	60	63	n.a.	PTFE	

n.a., not available; PTFE, polytetrafluoroethylene

bypass using the contralateral great saphenous vein, a long segment of which is mobilized, subcutaneously tunneled to the contralateral side, and anastomosed end-to-side with the common femoral vein on the affected side (24) (*Figure 2*). If no suitable great saphenous vein is found, ring-reinforced polytetrafluoroethylene prostheses can be used. To prevent bypass occlusion, this procedure is often combined with placement of an arteriovenous anastomosis. In the literature, the patency rate is reported to be 70% to 85% (follow-up: 6 to 216 months) (25, e10–e14).

In patients with more extensive venous obstructions (bilateral iliac vein obstruction, involvement of the infrarenal vena cava), femorocaval or ilio-caval prosthetic bypass is carried out (25, e15–e18).

The *Table* lists all the existing studies on open surgical treatment of postthrombotic syndrome. Based on the existing small studies, the AHA can only give a weak recommendation for the use of these bypasses (recommendation class IIb, evidence level C) (17).

Endovascular treatment of obstruction/occlusion

In 2000, Neglén et al. published the first study of the technique of percutaneous transfemoral recanalization of the iliac venous outflow tract by means of stent angioplasty (26). Since then, this treatment option has come into wider use. In 2007, Neglén et al. published the largest study so far, with 982 patients (n = 464 of

them with postthrombotic syndrome) in whom they carried out stent angioplasty of the iliac outflow tract. Mortality in the overall group was 0%; among the patients with postthrombotic syndrome, the primary patency rate after 72 months was 57% and the secondary patency rate was 86%. Ulcer healing was achieved in 58% of patients. Neglén et al. were able to show a significant improvement in quality of life (22). In other studies of treatment of postthrombotic syndrome using stent angioplasty, primary patency rates of 38% to 100% and secondary patency rates of 73% to 100% were achieved (follow-up: 9 to 68 months) (27, e19–e27). Complications (chiefly, thrombotic occlusion of the recanalized segment and hematomas at the catheter puncture site) were below 6% (22). Where recanalization failed, no progression of clinical signs occurred (22, 28). The AHA gives a weak recommendation for endovascular treatment (recommendation class IIb, evidence level B) (17).

Technical details

After venography and passage of the postthrombotically altered segment of the vein with wires and support catheters, the obstruction is dilated. Stent angioplasty is carried out, followed by further dilatation. The stent angioplasty is carried out along the entire postthrombotically altered iliac and caval segments (*Figure 3*).

Figure 3:

Intraoperative venography

- a) before recanalization (occlusion of the left pelvic venous outflow tract with demonstration of multiple collaterals)
b) after recanalization (good outflow via the stented left pelvic outflow tract, no collaterals are demonstrated)

Hybrid procedure

When inflow is obstructed by postthrombotic trabeculae in the region of the common femoral vein, in addition to stent angioplasty, surgical desobliteration (endovenotomy) of the common femoral vein and the ostia of its tributaries, especially the deep femoral vein, must be carried out. This ensures adequate inflow to the recanalized segment of vein and avoids early thrombotic occlusion: after longitudinal venotomy of the common femoral vein, the postthrombotic trabeculae are removed, and the venotomy is closed with a patch plasty. This technique was first published by Comerota et al. (n = 16 extremities with obstruction of the iliac veins and the common femoral vein). Mean follow-up time was 26 months. Quality of life and Villalta score improved significantly (29, e28, e29). Gloviczki et al. also achieved good results (e30). To improve inflow, additionally, an arteriovenous fistula can be created between the femoral vein and the superficial femoral vein; the fistula is then closed 6 weeks to 3 months postoperatively, in order to avoid right heart overload (e31–e33). On the basis of the existing studies, according to the AHA, the hybrid procedure may be considered in patients with severe postthrombotic syndrome (recommendation class IIb, evidence level C) (17) (Figure 4).

Contraindications

In cases where there is insufficient inflow from the periphery due to long-segment postthrombotic obstructions of the femoral and deep femoral veins, ilio caval recanalization is unlikely to succeed and is therefore contraindicated. In addition, patients in whom therapeutic anticoagulation is contraindicated should not undergo recanalization (30).

Peri- and postoperative concomitant treatment

After recanalization, thrombotic occlusion of the recanalized segment is the most frequent postoperative complication (1.5% during the early postoperative period [<30 days], 3% during the later postoperative period) (22). For this reason, adequate therapeutic anticoagulation during the perioperative period is essential (22, 27). Anticoagulation treatment should be continued for at least 6 months postoperatively, either with vitamin K antagonists (target INR: 2.5 to 3.5) or with the new oral anticoagulants (NOAC). Early mobilization and compression therapy should also be part of the postoperative treatment regimen (30, 31).

New venous stents

The stents usually employed for arterial stent angioplasty (e.g., Wall stents, nitinol stents) are unsuitable

Figure 4: Hybrid surgical procedure

- a) Schematic illustration of the hybrid procedure (iliac stent angioplasty, endovenectomy of the common femoral vein with patch plasty plus placement of a loop-shaped arteriovenous fistula (polytetrafluoroethylene prosthesis))
- b) Intraoperative site during endovenectomy of the left common femoral vein (status post longitudinal venotomy, guide wire in situ for the subsequent iliac stent angioplasty, evidence of postthrombotic trabeculae, marked with black arrows)

FV, femoral vein; CFV, common femoral vein; DFV, deep femoral vein; GSV, great saphenous vein

for stent angioplasty of a postthrombotically altered vein, as often long segments of the latter are fibrotic and often the vein is externally compressed (e.g., in May–Thurner syndrome). Venous stents with greater radial force have therefore been developed. High flexibility is also required, so that the stents can adapt to the anatomic course of the veins during movement; in the region of the iliac bifurcation, in particular, angulation up to 90° occurs during sitting (31, 32).

Results with venous stents

From March 2012 to July 2014, we carried out recanalization using venous stents (Sinus Venous Stent, Opti-Med, Ettlingen, Germany) in 40 patients with

postthrombotic syndrome. Follow-up time was 5.5 (1 to 18) months. Mortality was zero, and primary patency rates after 3, 6, and 12 months were 97%, 93%, and 85%. In three patients, rethrombosis occurred; these patients were successfully treated endovascularly. During therapeutic anticoagulation (Marcumar [phenprocoumon]: n = 15; rivaroxaban: n = 25), five patients experienced minor bleeding not requiring treatment. The mean Villalta score fell postoperatively from 11.5 (2 to 24) to 5.0 (0 to 16) (31, 32).

Surgical treatment of reflux

Incompetent venous valves in the common or deep femoral vein can be corrected by valve-reconstructing surgery (internal or external valvuloplasty, extravascular banding of the valve-bearing segment) (33, 34, e34, e35).

Where valves have been irreversibly destroyed, according to AHA recommendations, transplantation of an arm vein or vein transposition can be carried out (IIb, C) (17, 35, e36).

If, after successful recanalization of the obstructions, symptoms persist due to reflux because of secondary varicosis of the great saphenous vein, thermal ablation of the incompetent great saphenous vein is a possible approach (36, e37). However, no prospective studies have been carried out.

Stripping or ligation of perforating veins that are maintaining an ulcer because of reflux is aimed at alleviating symptoms and healing the ulcer. Only the diseased segments of veins are operated on (e38–e40). Neovalve construction is a potential approach for patients with refractory ulcers (IIb, C), (17, 37).

Discussion

Because of low case numbers, heterogeneous patient groups, and differences in treatments, no large randomized studies of operative treatment of postthrombotic syndrome exist of the kind that could provide a basis for clear, evidence-based treatment recommendations. The 2008 guideline of the German Society of Vascular Surgery is now out of date (38). The AHA, in its current guideline published in 2014, gives all operative treatments equally a weak recommendation (IIb) (17). For this reason, all conservative treatment options (compression by medical compression stockings or intermittent pneumatic compression, exercise training, physiotherapy) should be tried first. If severe symptoms of postthrombotic syndrome persist and the patient's quality of life is markedly impaired, especially by venous claudication and/or a venous ulcer that is not healing, indicating that conservative treatment has failed, surgical treatment should be considered. The decision whether to operate, and the choice of procedure, should be made with great care. The decision is made on a case-by-case basis taking account of the severity of the postthrombotic syndrome, the underlying pathology, and the patient's concomitant diseases. Since postthrombotic syndrome is very rarely a threat to life or limb, any operation carried out should

be the least invasive possible, with the aim of alleviating symptoms and improving quality of life. For this reason, endovascular recanalization appears to be an appropriate form of treatment; if it fails, no progression of symptoms occurs and open surgery remains as a further option (22, 26). Because the outcome of both open and endovascular procedures depends on operator expertise, these treatments should be carried out in a specialized vascular center offering the complete range of diagnostic investigations and surgical procedures including both endovascular and open surgery (17). Overall, the recommendations for the treatment of post-thrombotic syndrome rest on low level evidence. For definitive evaluation and optimization of treatment, therefore, prospective randomized studies of endovascular therapy of postthrombotic syndrome and optimal stent configuration are needed.

KEY MESSAGES

- Postthrombotic syndrome occurs in about 20% to 50% of patients in whom deep vein thrombosis has been diagnosed, and has considerable socioeconomic consequences.
- The following therapeutic options exist:
 - a) Conservative treatment
 - b) Open surgical procedures
 - c) Endovascular recanalization and hybrid procedures.
- Only when conservative treatment has failed should an invasive procedure be considered.
- Since at present there is insufficient evidence to show any procedure to be superior, the least invasive procedure possible should be employed.
- This suggests that endovascular recanalization may be regarded as the treatment of choice for chronic iliac vein obstruction.

Conflict of interest statement

Dr. Jalaie has received consultancy fees from Optimed. He has been reimbursed for conference, travel, and accommodation costs and received lecture fees from Optimed and Ab Medica.

Dr. Grommes has been reimbursed for conference, travel, and accommodation costs by Ab Medica. He has received lecture fees from Ab Medica and BTG UK. He has received funding to conduct a clinical trial from Ab Medica.

The remaining authors declare that no conflict of interest exists.

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