Thrombectomy and thrombolysis for the prevention and treatment of postthrombotic syndrome

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Postthrombotic syndrome (PTS) is a frequent complication of lower-extremity deep vein thrombosis (DVT), occurring in approximately 40% of patients despite the use of anticoagulant therapy. PTS causes significant impairment of patients' health-related quality of life, and no evidence-based therapies have been consistently effective. Catheter-directed thrombolysis and thrombectomy have been shown to remove acute thrombus, and it has been hypothesized they could prevent or reduce PTS. However, because these procedures can be associated with complications, mainly bleeding, randomized trial data are needed to determine when they should be used. In this article, I summarize the current status of thrombus removal procedures for DVT to provide contemporary guidance to clinicians seeking to individualize treatment decisions for their patients.

Learning Objectives

- Summarize the appropriate use of thrombectomy and thrombolysis for patients with acute DVT and established PTS
- Describe available multicenter randomized trials that have evaluated the use of catheter-directed interventions for the prevention and treatment of PTS

Introduction

Deep vein thrombosis (DVT) is associated with important early and late sequelae for patients. Best known is the predilection of DVT to cause pulmonary embolism, which can be fatal, and late episodes of recurrent venous thromboembolism (VTE). In addition, acute DVT causes pain, swelling, and activity limitation in the short term, and approximately 50% of patients with proximal DVT develop postthrombotic syndrome (PTS) within 2 years.[1,2] Because PTS can cause major disability, venous ulcers, and major impairment of health-related quality of life (QOL), its prevention and treatment are important to patients.

Since the early 1990s, catheter-directed thrombolysis (CDT) has been used in patients with severe manifestations of acute DVT to remove thrombus, relieve acute symptoms, and provide limb salvage.[3] On the basis of the historical experience with systemic thrombolysis and surgical thrombectomy, as well as early experiences with CDT, physicians have hypothesized that early endovascular thrombus removal may prevent or reduce PTS and help in preserving patients' long-term QOL.[4-6] However, these procedures also involve risks (especially major bleeding), patient inconvenience, and substantial resource use. The purpose of this article is to update the reader on the contemporary use of CDT and thrombectomy for the prevention and treatment of PTS.

PTS

Anticoagulant therapy is the mainstay of treatment for acute DVT because it has been shown to reduce the risk of symptomatic nonfatal and fatal pulmonary embolisms, thrombus extension, and VTE recurrence.[7] However, anticoagulation does not actively eliminate thrombus that has already formed. The thrombus often exhibits incomplete resolution, which causes obstruction to blood flow, and the accompanying inflammatory response can permanently damage the venous valves, leading to valvular incompetence.[8,9] These factors result in ambulatory venous hypertension and the clinical findings of PTS.[10]

Prospective studies have indicated that PTS develops in approximately 50% of patients who experience a first episode of symptomatic, proximal lower-extremity DVT.[1,2] PTS is a chronic condition that most commonly causes daily limb pain/aching, fatigue, heaviness, and/or swelling. Many patients with PTS experience only mild interference with their daily activities. However, in a minority of patients, painful venous claudication, stasis dermatitis, subcutaneous fibrosis, and/or skin ulceration may develop.[11] For these reasons, the presence and severity of PTS have been identified as leading predictors of the QOL of a patient with DVT 2 years after diagnosis.[2]

Unfortunately, prevention of PTS has remained an underappreciated and elusive goal of treatment. Poor-quality anticoagulation during the early months after DVT seems to correlate with an increased risk for developing PTS, but even under optimal circumstances, anticoagulation alone is not sufficient to protect many patients from this condition.[12] A subgroup analysis of 1 randomized trial suggested that use of a low molecular weight heparin (tinzaparin) may be superior to oral warfarin in preventing PTS, but this finding has not been confirmed prospectively, and the methods of PTS assessment in that study were suboptimal.[13] To date, rigorous prospective assessment of the effect of direct-acting oral anticoagulants on PTS rates has not been performed.

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Off-label drug use: Thrombolytic drugs for DVT and stents for iliac vein use are off-label.

Although early studies suggested that the routine use of elastic compression stockings may help to prevent PTS, the most rigorous study performed did not confirm these findings.[14-16] Specifically, the SOX trial was an 806-patient multicenter, double-blind, placebo-controlled, randomized controlled trial. In this study, the routine use of elastic compression stockings did not influence PTS, QOL, or recurrent VTE compared with sham stockings (with low ankle pressure). Hence, the best available evidence suggests that elastic compression stockings do not prevent PTS.

The anatomic extent of DVT seems to be an important predictor of a patient's risk of developing PTS. Specifically, patients with iliofemoral DVT (defined as DVT involving the common femoral vein and/or iliac vein, with or without involvement of other veins as well) experience recurrent VTE twice as frequently as patients with less extensive proximal DVT or isolated calf DVT and have significantly more frequent and more severe PTS.[1,17]

The use of systemic thrombolytic therapy to treat acute proximal DVT has been carefully assessed in randomized clinical trials. Although partial clot removal efficacy was demonstrated, and 2 small follow-up studies with major methodological limitations did suggest a reduction in PTS, major bleeding was increased by 3 to 4 times over anticoagulation alone.[4,5,18] Therefore, systemic thrombolytic therapy is not recommended for the treatment of DVT.

CDT

CDT refers to the direct intrathrombus administration of a fibrinolytic drug via a catheter or device embedded within the thrombus using imaging guidance.[19] The theoretical advantages of intrathrombus infusion are several: 1) clot removal efficacy is enhanced by the ability to achieve a high intrathrombus drug concentration and avoid bypass of the drug around the occluded veins; 2) the improved efficacy may enable reduced thrombolytic drug dose, treatment time, hospital resource use, and bleeding complications; and 3) catheter access into the venous system may enable treatment of underlying venous anatomic abnormalities (eg, May-Thurner syndrome), which may help to reduce the risk of recurrent DVT.[20]

It has long been known that CDT can enable rapid reduction of thrombus burden and restoration of venous patency. However, any use of fibrinolytic drugs is associated with a small but real risk of bleeding complications. In an early, 473-patient CDT registry, venogram analysis demonstrated that 85% of patients with acute DVT experienced >50% thrombus removal with CDT and that patients with symptom duration beyond 10 to 14 days were much less likely to experience clot lysis.[21] This study did not evaluate patients' long-term outcomes or any symptom or functional outcomes. However, major bleeding occurred in 11.4% of treated patients, and 0.4% of treated patients experienced an intracranial bleed. In addition, the mean treatment time was 53.4 hours, during which patients received close monitoring in an advanced-care unit. This study showed the earliest methods of CDT to represent a promising treatment, but with major disadvantages in terms of safety and resource use.

Three nonrandomized prospective studies compared the use of CDT and anticoagulant therapy vs anticoagulant therapy alone. In a registry-based study that compared 68 patients with acute iliofemoral DVT who underwent successful CDT with 30 retrospectively matched controls who received anticoagulation alone, the CDT recipients had fewer PTS symptoms and superior health-related QOL at mean 16-month follow-up.[22] In a prospective nonrandomized study in which 51 patients with acute iliofemoral DVT were permitted to choose to receive adjunctive CDT plus anticoagulation or anticoagulation alone, the CDT recipients had more frequent 6-month venous patency (83% vs 24%; $P < .0001$) and 5-year symptom resolution (78% vs 30%; $P = .0015$).[23] In a small, single-center randomized trial (n = 35) evaluating adjunctive CDT for acute iliofemoral DVT, at 6 months CDT recipients had a higher rate of normal vs function (72% vs 12%; $P < .001$) and less valvular reflux (11% vs 41%; $P = .04$).[24] However, these studies were limited by methodological imperfections that included single-center performance, small sample size, age differences between the cohorts being compared (potentially reflecting selection bias resulting from the nonrandomized design), and reliance on surrogate indicators of success (physiological testing) rather than validated measures of clinically important PTS or QOL.

In a multicenter randomized controlled trial (the CAVENT study) of patients with acute DVT involving the iliac and/or upper femoral venous system, CDT with anticoagulant therapy and compression was associated with a 26% relative reduction in the risk of PTS over 2 years (41.1% vs 55.6%; $P = .04$) compared with anticoagulant therapy and compression alone.[25] When the study was extended to 5-year follow-up, the benefit of CDT seemed to further increase (70% vs 42%; $P > .01$).[26] In this study, 3% of patients receiving CDT had a major bleed, including 1 who required surgery and another who received a blood transfusion, but there were no intracranial bleeds or deaths. Limitations of this study included its modest sample size (efficacy outcomes reported in 189 patients) and geographical limitation (4 treatment centers in Norway). Perhaps more importantly, beyond 6 months, there was no difference in health-related QOL between patients in the 2 treatment groups, leading to the suggestion that perhaps CDT simply prevented mild cases of PTS.[26,27] In any case, clinical practice guidelines continue to recommend against the routine first-line use of CDT for DVT.[7]

Evolution of CDT methods

The disadvantages of CDT in terms of safety and efficiency have been recognized for many years and have prompted a number of refinements, with the goal of reducing risk (ie, minimizing exposure to the thrombolytic drug) and treatment time. First, because early studies suggested that more than half of major bleeds consisted of bleeding at the venous access site, ultrasound-guided puncture has been routinely incorporated into clinical practice.[21] This good practice reduces the potential for inadvertent arterial punctures that can result in nontrivial bleeding. Second, whereas early studies used partial thromboplastin time (PTT) targets within the full therapeutic range, currently most practitioners deliberately dose unfractionated heparin (UFH) to target a subtherapeutic PTT during administration of the thrombolytic drug. Methods for this have included the use of a PTT target of 1.2 to 1.7 times the control and the use of reduced weight-based UFH dosing at 6 to 12 units/kg per hour. Some physicians use twice-daily low molecular weight heparin injections in lieu of UFH. Either way, the key point is to avoid a supratherapeutic PTT during thrombolytic drug exposure. Third, patient selection has become more conservative in terms of avoiding use of CDT in patients with risk factors for bleeding. Fourth, physicians have become more comfortable with placing stents in the iliac vein, both to treat obstructive stenosis and to manage residual thrombus as an alternative to continuing the thrombolytic infusion.[28] Collectively, it is believed that these measures may serve to reduce the risk of bleeding with CDT.

Table 1. Recommendations for use of CDT and PCDT

Factor	Consider CDT/PCDT	Do not use CDT/PCDT
Risk of bleeding	No bleeding contraindications	Active bleeding; recent obstetrical delivery; recent (<7-14 days) major surgery, trauma, or other invasive procedure; previous hemorrhagic stroke or presence of lesions in critical locations like central nervous system; uncontrolled hypertension
Clinical severity	Acute limb threat (urgent) or rapidly progressive IVC thrombosis; severe symptoms/physical limitation despite initial anticoagulation	Routine first-line DVT therapy with nonthreatened limb; asymptomatic or mildly symptomatic
Anatomic extent	Iliofemoral DVT (higher risk for PTS and severe PTS)	DVT limited to calf, popliteal, femoral veins
Symptom duration	Acute: <14 days (clot likely to lyse)	Chronic: >28 days (clot will not lyse)
Other factors	Life expectancy >l year; walked at baseline; few comorbidities	Age >65 years; nonambulatory before the DVT; many comorbidities

IVC, inferior vena cava.

In addition, CDT has been refined to incorporate device technology aimed at enabling faster delivery and intrathrombus dispersion of the fibrinolytic drug and thrombus aspiration. Ultrasound-assisted CDT involves the delivery of the fibrinolytic drug through a specialized catheter that also emits low-power ultrasound energy into the thrombus. The idea is that by loosening fibrin strands and thereby enhancing the surface area of thrombolytic drug exposure, thrombolysis may be hastened, enabling use of a reduced dose of thrombolytic drug. However, a small randomized trial did not find an added benefit to use of the ultrasound catheter compared with a standard multisidehole catheter.[29]

Percutaneous mechanical thrombectomy refers to the use of a catheter-based device that aspirates or macerates thrombus. Until recently, available percutaneous mechanical thrombectomy devices were not particularly effective in removing the large thrombus volumes commonly associated with DVT when used without a thrombolytic drug. One new method is worthy of mention. The AngioVac device (Angiodynamics) is a large suction thrombectomy catheter that has shown initial effectiveness in early case series in removing large-volume acute thrombus from the inferior vena cava and right atrium in patients who are ineligible to receive CDT.[30] Although no prospective studies have been completed with this device, it seems likely to offer a new option for some of the most challenging patient cases of DVT. However, because the device requires 2 large sheaths to be placed in the jugular and/or common femoral veins (generally requiring surgical closure), creating a cardiopulmonary bypass circuit, it is not suitable in its current form for routine use for iliofemoral DVT.

Pharmacomechanical CDT (PCDT) involves the use of catheter-mounted thrombectomy devices along with intrathrombus delivery of fibrinolytic drugs, with the idea that the combination can enable faster thrombus removal with reduced drug dose.[16] With some methods, some patients with DVT can have complete thrombus removal in a single procedure session, rather than requiring 1 to 2 days of drug infusion with advanced-care unit monitoring.[31,32] Although retrospective studies have suggested that PCDT is associated with reductions in drug dose and treatment time compared with infusion-only CDT, there have been no completed published multicenter RCTs evaluating PCDT.[33] The National Institutes of Health–sponsored ATTRACT trial, which was recently completed, will soon provide rigorous data on the benefit-to-risk ratio of PCDT.[34] In this study, patients with acute proximal DVT were randomly assigned to receive PCDT together with anticoagulation and compression vs anticoagulation and compression alone, with PTS, QOL, safety, and cost assessed over 2 years. The results of this pivotal study are expected this year. Recommendations for the judicious use of CDT and PCDT are presented in Table 1.[35]

Treatment of established PTS

Patients with PTS often experience significant pain, activity limitation, and impairment of QOL. Measures that are sometimes recommended include lifestyle modifications (eg, periodic leg elevation, exercise, smoking cessation, weight loss), medical therapy (eg, anticoagulation, pentoxifylline, diuretics, venoactive medications), compressive strategies (eg, stockings, home edema pumps, wearable compression devices), and in some cases surgery (eg, debridement of ulcers, venous bypass procedures).[36] However, because few treatment strategies for established PTS have been subjected to rigorous clinical study, there is a lack of evidence-based management options.

For any patient with PTS, it is first important to confirm the diagnosis of PTS and to consider if the clinical severity of the disease merits an aggressive treatment approach. Fundamental elements of the clinical approach include a medical history and physical examination, duplex ultrasound to evaluate for signs of iliofemoral venous obstruction or saphenous venous valvular reflux, and careful verification that key elements of low-risk conservative therapy have been used (eg, anticoagulation appropriate for the DVT history, compression, and professional wound care for venous ulcers).

Because chronically occluded veins usually are composed mainly of collagen rather than fibrin, there is probably little role for fibrinolytic drugs in the management of established PTS. However, 2 physiological elements are often amenable to correction with other endovascular procedures: 1) iliac vein obstruction is amenable to stent placement (although no devices have been US Food and Drug Administration approved for this indication in the United States at the time of writing), which can enhance outflow and thereby reduce venous pressures; and 2) saphenous vein reflux is amenable to endovenous thermal (radiofrequency or laser) ablation; this eliminates an additional pathway for downward transmittal of venous pressures. These treatments can be delivered to most patients in outpatient procedure centers with use of conscious sedation, without interruption of ongoing anticoagulation.

Preliminary studies of low-quality methodology have suggested that improvement of pain, swelling, and venous ulcer healing may occur

in approximately 70% of patients with PTS who are treated with iliac vein stent placement.[37] However, because this has not been confirmed in prospective comparative studies, and because stents may be associated with recurrent thrombosis or other long-term risks as yet unknown, stent implantation should be targeted to those patients in most need of benefit and only after conveying the risks and uncertainties to these patients. Intractable pain, massive edema, progression of skin changes, and venous ulcer formation are among the better-justified indications for intervention.

Patients who either have a patent iliac vein or continue to experience lifestyle-limiting PTS symptoms after stent placement should undergo repeat duplex ultrasound to evaluate for saphenous vein reflux. If present, endovenous thermal ablation (EVTA) can be used to eliminate the refluxing superficial vein. EVTA involves the delivery of thermal energy to the vein wall with a specialized catheter, resulting in irreversible fibrosis and resorption of the vein. This procedure tends to be durable in patients with primary valvular insufficiency, but it has not been robustly studied in patients with PTS. Two retrospective studies that evaluated treatment strategies combining iliac vein stent placement with EVTA reported favorable outcomes in terms of relief of pain, relief of swelling, and ulcer healing.[38,39] Of note, these studies were relatively small, lacked control groups, and had a number of methodological limitations that conferred a high potential for bias. Rigorous prospective studies of PTS treatment by multidisciplinary investigator groups are currently in development.[40]

In conclusion, catheter-based interventions have substantial potential to improve treatment outcomes in severely affected patients with acute DVT and established PTS. The use of CDT as upfront adjunctive therapy for patients with acute proximal DVT is being evaluated in pivotal randomized trials. Studies evaluating endovascular therapy strategies for established PTS are also in development.

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