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CATHETER-DIRECTED THROMBOLYSIS TO AVOID LATE CONSEQUENCES OF ACUTE DEEP VEIN THROMBOSIS

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Abstract

The application of catheter-based methods to treat acute deep vein thrombosis (DVT) has increased in recent years. Catheter-directed thrombolysis (CDT), introduced during the early 1990s, has shown the ability to rapidly eliminate thrombus and is used in many centers as a salvage therapy for DVT patients who exhibit a poor initial response to anticoagulant therapy. However, CDT has disadvantages in terms of safety and resource use. Although CDT methods have evolved substantially to try to address these issues, for most of the last 25 years there was little high-quality data on CDT outcomes upon which to base patient care decisions. The paucity of evidence was particularly problematic for long-term outcomes such as recurrent venous thromboembolism (VTE) and the post-thrombotic syndrome (PTS). Fortunately, rigorous studies of CDT are now being completed. Accordingly, the purpose of this article is to: 1) state the known and unknown factors influencing risk and benefit with use of CDT and related methods to treat acute DVT; 2) summarize emerging evidence showing the patient outcomes that occur when CDT is used for first-line management of DVT; and 3) suggest clinical parameters for CDT utilization in light of the available evidence.

Keywords

deep vein thrombosis; catheter-directed thrombolysis; post-thrombotic syndrome; venous thromboembolism; pharmacomechanical; stent

Introduction

There currently exists among many physicians an appreciation for the concept that the initial treatment of acute deep vein thrombosis (DVT) may meaningfully influence the patient's long-term outcome. However, despite the introduction of new options for anticoagulant

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Conflict of Interest Statement

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therapy into clinical practice, DVT continues to exert an important and negative impact upon the health status of affected patients, even years after the initial diagnosis (1, 2). Even with the administration of anticoagulant therapy, DVT recurs with moderate frequency and often results in the post-thrombotic syndrome (PTS) (2–4). For many years, gaining consensus on the actual incidence of PTS after DVT was challenging to achieve due to the availability of widely varying measurement scales. However, contemporary, prospective studies suggest that PTS occurs in approximately 25–50% of patients with first-episode, proximal lower extremity DVT. PTS commonly causes daily limb swelling, pain, heaviness, and fatigue of the involved extremity. Patients with moderate-to-severe PTS may develop short-distance venous claudication, stasis dermatitis, irreversible skin changes, venous leg ulcers, and major impairment of quality of life (QOL). Unfortunately, established PTS lacks evidence-based therapy that can reliably reduce symptoms and improve limb function and QOL.

Catheter-based thrombolysis (CDT) and related methods have been utilized in the management of DVT since the early 1990s (5–8). While they have become accepted to a degree in some centers for salvage treatment of patients with the worst acute DVT manifestations, only recently have they undergone rigorous evaluation for first-line use in multicenter randomized controlled trials (RCTs). The objectives of this chapter are several: 1) to state the rationale, risk-benefit-ratio, and uncertainties associated with use of CDT and related methods to treat acute DVT; 2) to summarize emerging evidence showing the patient outcomes that are observed when CDT is used for DVT; and 3) to suggest clinical parameters for CDT utilization in light of the available clinical trial data.

The Open Vein Hypothesis

The baseline factors that predispose a patient to develop PTS are not yet entirely understood but include recurrent ipsilateral DVT, poor quality initial anticoagulant therapy, greater thrombus extent (proximal DVT > isolated calf DVT; and iliofemoral DVT [involvement of the common femoral or iliac vein] > calf or femoral-popliteal DVT), higher age, female gender, and elevated body mass index, based on prospective studies (2, 3, 9–11).

Although less well-studied prospectively, historical studies have identified associations between the most severe manifestations of PTS and ***ambulatory venous hypertension*** (which was directly measured in some) (12). Ambulatory venous hypertension, in turn, is thought to be the result of a combination of venous obstruction (due to residual thrombus and venous scarring) and valvular reflux (13–17). Under usual conditions, the venous valves protect the lower limb from hydrostatic pressure. However, the inflammatory response to acute DVT damages the venous valves, and even uninvolved veins may enlarge and show valve leaflet separation, leading to valvular incompetence. Longitudinal ultrasound studies have shown that veins that show spontaneous clot lysis after DVT are less likely to develop valvular incompetence (15).

In terms of venous obstruction, a higher risk for recurrent VTE and PTS appears to be present when residual venous thrombus exists after a course of anticoagulant therapy for DVT (17–19). For patients with DVT that does not extend above the thigh veins, recanalization over time is the norm. On the contrary, in patients with iliofemoral DVT,

complete recanalization is a relatively rare occurrence, which may to some degree account for why these patients appear to develop PTS with greater frequency and severity (3, 11).

In small randomized trials, the administration of fibrinolytic drugs from a peripheral intravenous line enabled complete or partial clot lysis much less frequently than anticoagulant therapy alone (20). Reduced rates of PTS were observed in the thrombolysis-treated patients, but these studies were small, did not utilize validated measures of PTS, and had other design issues (21, 22). In a randomized trial, iliofemoral DVT patients who were treated with contemporary surgical thrombectomy and anticoagulation showed improved long-term limb outcomes than patients treated with anticoagulation alone (23). However, surgical thrombectomy and systemic thrombolysis cannot be widely employed for DVT because of the attendant risks which included substantial rates of bleeding and re-thrombosis.

Catheter-Directed Thrombolysis (CDT)

Catheter-directed thrombolysis (CDT) refers to the delivery of a fibrinolytic drug directly into the thrombus using a catheter or catheter-based device that is embedded within the thrombus using imaging guidance (24). Direct intra-thrombus drug delivery enables the potential to obtain a higher local drug concentration than systemic thrombolysis with use of a reduced dose, treatment time, hospital resource utilization, and bleeding complications (25, 26).

The traditional method of infusion CDT is as follows: a) ultrasound-guided access into a lower extremity vein (usually the popliteal vein or the posterior tibial vein); b) diagnostic catheter venography to define the extent of thrombus; c) infusion of a fibrinolytic drug directly into the DVT through a multi-sidehole catheter (5–7). Usually this is recombinant tissue plasminogen activator (rt-PA, Genentech, South San Francisco, CA); however, at present, no fibrinolytic drug has an FDA approval for DVT treatment. The dosing that has been used in randomized trials is a continuous infusion at 0.01 mg/kg/hr, not to exceed 1.0 mg/hr (27, 28). During the treatment period, intravenous unfractionated heparin with a subtherapeutic target, or low molecular weight heparin, is given. The patient is closely monitored in an advanced-care unit, with discontinuation of the drug if bleeding occurs. Patients undergo repeat venography at 6–24 hour intervals thereafter. When complete or near-complete thrombus removal is achieved, any visualized obstructing lesions (e.g. left common iliac vein stenosis from May-Thurner Syndrome, or other areas of scarring in the vein) are managed with balloon venoplasty or stent placement (5). The sheath is removed, full-dose anticoagulation is re-initiated, and the transition to long-term oral anticoagulant therapy is undertaken.

In early case series and a prospective multicenter registry of 473 patients who received urokinase CDT, 50% clot lysis was observed to occur in 80%–90% of acute DVT patients with duration of symptoms < 14 days (6). However, major bleeding occurred in 5–12% of patients, with approximately 0.4% suffering intracranial bleeding. Symptomatic PE was very infrequent (1.3%) and fatal PE was rare (0.2%). The typical CDT infusion took around 48–

72 hours to complete, which given the advanced-care unit monitoring is a large use of resources.

Three subsequent non-randomized prospective studies compared the use of CDT and anticoagulation versus anticoagulation alone, observing fewer PTS symptoms and better health-related QOL, venous patency, and/or venous valve function in the CDT recipients. However, these studies had major design limitations, including selection bias (e.g., significant age differences in one study reporting a difference in QOL, and patients' ability to choose which therapy they received in another study), small sample size, non-randomized design (two of the three), performance in a single center, and lack of use of validated measures of PTS (29–31).

The Catheter-Directed Venous Thrombolysis (CaVenT) Study was a multicenter RCT performed to evaluate CDT for acute proximal DVT. In this study, 2-year outcomes were reported in 189 patients with femoral or iliac DVT who received standard DVT therapy with randomization to receive or not receive additional CDT. The CDT protocol in this study did not include use of percutaneous mechanical thrombectomy devices, which is different from contemporary U.S practice. The primary outcome measure for this study was the Villalta Scale, which assesses 5 symptoms and 6 clinical signs of PTS. The use of CDT was associated with reduced 2-year PTS (56% versus 41%, $p = 0.047$) (27). Approximately 3% of CDT-treated patients had major bleeding, with none suffering lasting consequences. Although the change in health-related QOL from baseline to 6 months was slightly greater in the CDT patients, especially those with a patent venous system, there was no significant difference in the change in QOL from baseline to 2 years; also, there was no difference in recurrent VTE rates (32). Given the demonstrated relationship of PTS and QOL in previous DVT studies, it is unclear if the absence of an observed QOL difference in CaVenT reflected its limited statistical power versus a true lack of effectiveness for CDT. A subsequent study using the CaVenT data concluded that CDT was cost-effective, with CDT costing \$20,429 per quality-adjusted life-year gained (80% likelihood of being cost-effective at a willingness-to-pay threshold of \$50,000) (33). As this study was performed in Norway, the extent to which these findings can be extrapolated to other countries' health systems is unclear. However, of further interest is the fact that followed out to 5 years, the difference in PTS rates increased further but QOL was still no different (34).

These findings provided support for the open vein hypothesis, but the modest size of this study and the lack of an effect upon patients' long-term QOL may have tempered its overall impact upon clinical practice. In addition, the disadvantages of CDT when applied to a real-world population were highlighted by a propensity-matched comparative study using the National Inpatient Sample database (35). In this population of DVT patients, the use of thrombolytic therapy was associated with higher blood transfusion rates (11.5% versus 6.5%, $p < 0.001$), more intracranial bleeds (0.9% versus 0.3%, $p = 0.03$), longer length of stay (7.2 versus 5.0 days, $p < 0.001$), and higher hospital charges (\$85,094 versus \$27,604, $p < 0.001$). This comparison was burdened by the limitations of sampling administrative databases, the lack of data on treatment efficacy (e.g. PTS rates), and some degree of selection bias since the patients selected for CDT may not have been sufficiently similar to those who were not selected for CDT for at least some relevant attributes, even with the

propensity matching. Nevertheless, these findings argue for caution in recommending large-scale, first-line use of CDT for DVT.

Ultrasound-Assisted Thrombolysis

The original infusion CDT method involved fibrinolytic drug delivery through a standard multi-sidehole catheter. In contrast, a specialized catheter that provides intra-thrombus drug infusion while simultaneously applying low-power ultrasound energy (EKOS, Bothell, WA) to improve drug dispersion is favored by some practitioners. However, the additional ultrasound energy has not been shown to provide any incremental short-term or long-term benefit in DVT patients. The BERNUTIFUL Study was a pilot RCT that enrolled 50 acute iliofemoral DVT patients who were felt to need CDT on clinical grounds to be treated using the EKOS catheter and a standardized fibrinolytic dosing regimen (36). The patients were randomized to have, or not have, the ultrasound energy turned on. There was no difference in clot removal efficacy, major bleeding, or PTS (37). Hence, the limited available evidence does not support this catheter as providing additional benefit in either efficacy or safety for acute DVT treatment.

Pharmacomechanical Catheter-Directed Thrombolysis (PCDT)

Pharmacomechanical catheter-directed thrombolysis (PCDT) represents the combination of intra-thrombus fibrinolytic drug administration with concomitant percutaneous mechanical thrombectomy devices aimed at improving drug penetration and thrombus maceration and aspiration (24). The thrombectomy devices can be used after an initial rt-PA infusion to reduce the need for long-duration infusion, or as a way to achieve treatment in a single 1–3 hour procedure session (without the need for long drug infusions or ICU monitoring) (38, 39). For example, with the “powerpulse” technique, the Angiojet Rheolytic Thrombectomy Catheter (Boston Scientific, Marlborough, MA) can pulse-spray drug into the thrombus, after which it can aspirate the remaining thrombus (40).

With greater awareness of the impact of PTS upon patients’ lives, the availability of PCDT methods that appear to allow more efficient treatment, and ongoing concerns about the safety and long-term effectiveness of these methods, societal clinical practice guidelines have been divided in terms of whether and when CDT and PCDT should be recommended for use. The 2016 American College of Chest Physicians’ VTE Treatment Guideline Update (41) recommended against first-line use of CDT/PCDT, whereas guidelines of the American Heart Association, Society of Interventional Radiology, Society for Vascular Surgery, and American Venous Forum have suggested that it may be reasonable to offer to carefully selected patients with acute iliofemoral DVT who are expected to be at low risk for bleeding (8, 42–44).

This state of clinical equipoise led to the development and completion of the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) Study, a NIH-sponsored, Phase III, randomized, 56-center, open-label, assessor-blinded, controlled clinical trial (28). 692 patients with acute DVT involving the femoral, common femoral, and/or iliac vein were randomized to receive PCDT + standard

therapy (anticoagulation and compression) versus standard therapy alone, and were followed for 2 years. The primary study results (occurrence of PTS at 2 years) are expected to be published soon. In addition, further studies are planned to analyze PTS severity, QOL, and costs in detail, with particular reference to the iliofemoral DVT and femoral-popliteal DVT subgroups.

Patient Selection for CDT and PCDT

Patient selection for CDT or PCT should be individualized, with careful consideration of duration of symptoms, the anticipated risk of bleeding, life-expectancy, and expected activity level, as well as his/her willingness to undergo a minimally-invasive catheter-based procedure.

Successful endovascular treatment of acute DVT is most likely when symptoms have been present for less than 14 days (6). Patients with acute iliofemoral DVT are known to have a higher frequency and severity of PTS, and are more likely to have an underlying stenosis; hence, these may be the patients most likely to benefit. In general, CDT/PCDT is suggested for patients with acute limb-threatening circulatory compromise, or for non-threatened patients with iliofemoral DVT who have particularly severe symptoms despite initial anticoagulation. The latter suggestion is made based upon the known efficacy of CDT/PCDT for removing thrombus, clinical observations of improved symptom status, and the suggestion from the available studies that CDT/PCDT may influence PTS. However, because of those studies' methodological limitations, confidence in the last observation is limited at present. Patients with short life-expectancy, low activity level, or elevated bleeding risk (e.g. recent surgery, trauma, or obstetrical delivery; intracranial lesions; thrombocytopenia) are poor candidates, as are patients with DVT that is chronic (CDT ineffective) or asymptomatic (rarely develop PTS) (6, 45). It is hoped that the ATTRACT Trial and other studies of CDT/PCDT will enable greater understanding of the effects of CDT/PCDT and more confident recommendations.

Conclusion

CDT and PCDT offer rapid thrombus removal and, likely, faster relief of initial acute DVT symptoms compared with anticoagulation alone, at the price of an increase in major bleeding and the rare risk of devastating bleeding. One rigorously conducted multicenter randomized controlled trial suggests that CDT may reduce PTS, but the absence of data showing a compelling effect upon long-term QOL argues for caution in using these methods as first-line therapy for proximal DVT. Additional studies are expected and pending their results, patient selection should be carefully individualized to promote safety and maximize clinical benefit. Overall, we suggest that use of CDT/PCDT should be limited to patients with acute iliofemoral DVT, low projected bleeding risk, and either a) acute limb threatening circulatory compromise from DVT; or b) severe/worsening ongoing symptoms, documented major thrombus progression, or signs of impending limb threat despite initial anticoagulation. It is hoped that new studies will soon enable more confident recommendations.

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Highlights

1. The initial treatment of acute DVT influences late complications.
2. Post-thrombotic syndrome affects 40% of patients with symptomatic DVT.
3. Catheter-directed thrombolysis (CDT) rapidly eliminates clot but increases bleeding.
4. Randomized trials are inconclusive on whether CDT provides long-term benefit.
5. A highly individualized approach should be used for patient selection.