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TREATING INFRAINGUINAL DVT

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Introduction

Catheter-directed thrombolysis (CDT) and related techniques have been employed most frequently in patients with acute iliofemoral DVT (1). However, as local comfort with this form of treatment increases, interventional radiologists who have developed a reputation for providing quality DVT care are increasingly referred many patients who do not meet the definition of the ideal patient. In many cases, referred patients have clinical factors that are believed to adversely influence the safety side of the equation, such as advanced age or relatively recent surgery. In other scenarios, patient subsets for whom a lower likelihood or degree of long-term benefit from CDT might be expected are referred, such as patients with acute-on-chronic DVT. The purpose of this article is to help the reader understand the risk-benefit proposition that CDT offers to patients with DVT that is limited to veins below the common femoral vein, to enable better and more individualized decision-making for patients.

Clinical Evaluation and Indications

Below are five important questions that should be asked when contemplating the use of endovascular thrombolytic therapies for patients with DVT of limited extent:

1. What is the highest anatomic extent of the DVT?

Lower extremity DVT has historically been described as “proximal” (i.e. highest thrombus extent in the popliteal vein or above), which carries a higher risk of symptomatic pulmonary embolism (PE), versus “distal” (i.e. isolated calf vein thrombosis). For both patient groups, anticoagulant therapy tends to be highly effective in preventing PE (2,3). Both groups are at risk of developing recurrent DVT and the post-thrombotic syndrome (PTS); however, patients with isolated calf DVT tend to be less symptomatic at presentation and are much less likely to develop PTS (4). Keeping in mind the 3% rate of major bleeding and the 0.4% risk of fatal or intracranial bleeding associated with use of CDT for carefully selected DVT

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patients, one must conclude that thrombolytic therapy cannot be justified for patients with isolated calf DVT (5–7).

The same is probably true of most patients whose DVT extends no higher than the popliteal vein. For most such patients, venous outflow from the limb is aided by a patent deep (profunda) femoral vein and collateral reconstitution of the more cephalad femoral vein. Although these patients may have a slightly higher risk of PTS than patients with isolated calf DVT, the added benefit of CDT over anticoagulation alone is not clear. It should also be noted that while the tibial veins can be used to access popliteal vein thrombus, there are technical challenges to restoring and maintaining patency of the smaller veins that are needed to provide inflow after thrombolysis. For these reasons, the incremental benefit of CDT in this group of patients is felt to be questionable, and it is notable that these patients were excluded from both recent/ongoing multicenter randomized controlled trials (RCTs) of endovascular DVT thrombolysis (CAVENT and ATTRACT) (5,8). Given the risk of serious bleeding, this author believes that benefit needs to be proven in randomized trials before such patients are exposed to the risks of treatment.

Patients with DVT extending into the femoral vein, but not the common femoral or iliac vein, are increasingly being considered for CDT. On the one hand, it should be clearly recognized that involvement of the femoral vein is very different than involvement of the common femoral or iliac vein (i.e. from iliofemoral DVT). Unlike the iliac vein, the femoral vein tends to recanalize endogenously over time in anticoagulated patients (9). Patients with femoral DVT can benefit from an open deep femoral vein, tend to be much less symptomatic at presentation, and are at significantly lower risk of both recurrent DVT and PTS than patients with iliofemoral DVT (3). In a prospective study of 1149 patients with symptomatic DVT, patients with IFDVT had a 2.4-fold increased risk of recurrent VTE at 3 months compared with patients with femoropopliteal DVT (10). In a prospective, multicenter, 387-patient study of patients with acute symptomatic DVT, patients with DVT involving the CFV or iliac vein had significantly increased frequency and severity of the post-thrombotic syndrome (PTS) over 2 years follow-up ($p < 0.001$) (3).

On the other hand, it is fair to observe that patients with DVT involving the upper half of the femoral vein constituted approximately half of the evaluated proximal DVT population in the CAVENT Study, which observed a significant reduction in PTS over 2 years follow-up in the patients randomized to adjunctive CDT (5). Unfortunately, although this RCT was rigorously conducted and provides the best currently available data on the use of CDT, patients were not stratified according to anatomic thrombus extent, and the outcomes of the femoropopliteal versus iliofemoral DVT subgroups were not separately presented. Hence, it is not known if either a) the 26% relative risk reduction in 2-year PTS (41.1% CDT versus 55.6% Control, $p = 0.04$) was comparable across patient subgroups with varying anatomic thrombus extent; or whether b) most of the benefit observed was limited to the iliofemoral DVT subgroup. In the ongoing NIH-sponsored ATTRACT Trial, patient randomization was stratified by whether or not the DVT involved the common femoral and/or iliac vein at baseline, which should permit robust subgroup analysis once the study is completed (8). Until then, in the author's view, it would be appropriate to avoid treating patients with DVT limited to the femoropopliteal segment or, at a minimum, to limit this practice to: a)

providers with a clear track record of success in treating iliofemoral DVT; and b) those patients who appear to be the most likely to benefit and least likely to be harmed. Some considerations in making this judgment are summarized below.

2. How symptomatic is the patient and how long have symptoms been present?

A careful medical history and physical exam are pre-requisites to considering aggressive therapy for DVT (7). The physician should attempt to pinpoint the start date of the current DVT episode, as well as the dates and anatomic locations of previous DVT episodes. Patients with asymptomatic DVT rarely develop PTS and generally should not receive CDT (11). Most patients with symptomatic DVT limited to the femoropopliteal segment will exhibit clinical improvement with initial anticoagulant therapy, obviating the need for aggressive therapy. Femoropopliteal DVT patients whose symptoms started more than 10–14 days previously are not likely to achieve complete lysis or sustained patency with CDT (6). Many patients with previous DVT, especially if in the popliteal vein below a newly thrombosed femoral vein, may experience initial improvement but patency may be difficult to maintain due to the compromised inflow. As a result, in the author's opinion, only carefully selected patients who continue to experience major limb pain and/or swelling that limit activity after an initial course (e.g. 5 days) of anticoagulant therapy should be considered for CDT when the DVT is limited to the femoropopliteal veins.

3. Are there other factors that might affect the risk of developing PTS?

The pathogenesis of PTS is incompletely understood, and its development is difficult to predict in individual patients with proximal DVT. Recurrent ipsilateral DVT is the known risk factor that is most closely associated with the development of PTS (3,12). Smoking and obesity are lesser risk factors for developing PTS (so is age > 65 years, but advanced age also likely adds to the bleeding risk with CDT) (13,14). If the limb swelling and pain involve both the thigh and the calf, or if the common femoral vein Doppler waveform shows reduced respiratory phasicity one of several anatomic factors might be present: a) occult thrombus in the iliac vein; b) intrinsic stenosis or extrinsic compression of the iliac vein (e.g. May-Thurner Syndrome); or c) thrombosis of the profunda or its tributaries. By limiting venous outflow, each of these factors might increase the risk of PTS and be readily reversible with endovascular intervention. On the other hand, the presence of an uninvolved duplicated femoral vein might reduce PTS risk. The presence of one or more factors that might increase PTS in a very symptomatic patient with acute femoropopliteal DVT might reasonably sway one towards a more aggressive treatment approach.

4. Are there factors that would increase the risk of bleeding or other complications?

All patients considered for thrombolytic therapy must undergo a careful clinical evaluation for factors that may increase procedural risks, including recent (< 7–14 days, depending on type) major surgery, obstetrical delivery (< 7 days), trauma, or other invasive procedure; the presence of bleeding-prone lesions in critical locations like the central nervous system; thrombocytopenia; advanced age; or severe dyspnea or other acute medical illness that would preclude a procedure in the prone position with conscious sedation (7). It should be remembered that the treatment of DVT is an elective procedure, in contrast to the use of thrombolytic drugs for patients with acute myocardial infarction, stroke, or massive

pulmonary embolism (PE). Given the uncertainties surrounding the risk-benefit ratio of CDT for DVT of limited extent, a very low threshold should be employed to exclude patients who are at increased risk of complications.

5. How functional was the patient before the DVT and how motivated is he/she now?

Femoropopliteal DVT patients selected for CDT should stand to benefit significantly from treatment and, in general, should have had normal or near-normal ambulatory capacity before the DVT occurred. In addition, it is very reasonable to include each individual patient's values and preferences in determining the therapeutic approach. Patients lysed for this indication should be highly motivated towards aggressive therapy, and the informed consent process should include a balanced discussion of the possible benefits, the possible lack of benefits, the risks, and treatment alternatives including that of simply switching to another anticoagulant regimen. For example, in some patients, the use of low molecular weight heparin (LMWH) monotherapy for a prolonged period may be effective in relieving persistent symptoms of acute DVT, presumably due to the anti-inflammatory properties of these agents and the more consistent anticoagulant effect they provide compared with oral warfarin therapy.

Equipment, Procedural Steps, and Technical Challenges

The endovascular treatment of acute femoropopliteal DVT is conducted using the same basic steps and equipment as for acute iliofemoral DVT: a) ultrasound-guided venous access, ideally using a micropuncture system; b) intrathrombus delivery of a thrombolytic drug using a traditional multi-sidehole infusion catheter or a specialized drug delivery device (see below); c) clean-up of residual thrombus; and d) treatment of any underlying venous stenosis (1,7). A few additional considerations specific to femoropopliteal DVT are summarized below.

First, since the DVT usually involves the popliteal vein, alternative options for venous access may be considered. The tibial veins (usually the posterior tibial vein) can be accessed under ultrasound guidance in many patients, and will generally afford good access for CDT. Potential disadvantages include occasional technical difficulty in gaining access due to vasospasm, and the fact that intramuscular bleeding may be more likely than with popliteal vein access (5). The small saphenous vein can be used - however, it is important to first examine it with ultrasound to confirm the location of its entry into the deep system, since a high entry (which occurs in over one-third of patients) will result in an inability to directly access the popliteal vein thrombus. Retrograde access via an internal jugular or common femoral vein can also be used, but traversal of the thrombus-bearing venous valves can be cumbersome. Hence, in many cases, puncture of the thrombus-containing popliteal vein may be the best option.

Second, as for iliofemoral DVT, the choices for drug delivery include traditional infusion-only CDT (i.e. no device use); ultrasound-assisted CDT (i.e. EkoWave catheter); and pharmacomechanical CDT (PCDT) techniques that include infusion-first PCDT (i.e. use thrombectomy devices after an initial course of CDT), isolated PCDT (i.e. using the Trellis), and power pulse-spray PCDT (i.e. using the AngioJet) (15–18).

Although there is no consensus on the optimal thrombolytic method to use, it is the author's belief that most patients with complete thrombotic occlusion of the entire popliteal vein segment may be best served with infusion-first PCDT via a multi-sidehole catheter. The potential benefits of this approach are that a) it is less mechanically aggressive than a device-based method involving more mechanical manipulation, which may be important in poor-inflow situations; and b) by allowing the thrombolytic drug to circulate systemically over at least several hours, it may be more likely to dissolve thrombus in important non-axial veins such as the deep femoral vein and tibial veins. In the U.S., infusion CDT will usually involve administration of 0.01 mg/kg/hr (maximum 1.0 mg/hr) of rt-PA (e.g. 50–100 ml/hr of a solution of 10 mg rt-PA in 1000 ml NS). An ultrasound CDT catheter may also be used for this purpose. When an ultrasound catheter is used, the catheter is positioned within the thrombus in the same fashion as a traditional multi-sidehole catheter. Dilute thrombolytic drug is infused through the catheter at a flow rate that should stay at or below 50 ml/hr (e.g. 50 ml/hr of a solution of 10 mg rt-PA in 500 ml NS will provide 1.0 mg/hr), and the ultrasound is activated by pressing a single button. Although ultrasound CDT has many proponents who believe that it speeds lysis, there is limited data to support this belief and the only published comparative study (which had methodological limitations from its retrospective nature) did not find any advantage to its use (19).

Though not proven to prevent PTS yet, PCDT may also be used to obtain faster treatment with a reduced drug dose, especially in patients in whom a thrombus-free segment of popliteal vein can be identified. With Isolated PCDT, an 8 French sheath is placed into the access vein. A Trellis-8 catheter (either 15 cm or 30 cm infusion length) is positioned across the thrombus-containing vein segment and its two catheter-mounted occlusion balloons inflated to “isolate” the segment. A stepped infusion of rt-PA (dose depends upon thrombus extent – in the ATTRACT Trial protocol, 1 mg rt-PA per 3–4 cm clot length is used which generally results in 4–10 mg for the initial delivery) is delivered during a 10-minute period during which the internal oscillation wire is activated to disperse the drug. At the operator's choice, some of the rt-PA remaining in the isolated segment may then be removed via the device's aspiration port. In general, two 10-minute spins are performed in all thrombus-containing areas (which can mean up to 4 spins if the thrombus exceeds 25–30 cm in length). With PowerPulse PCDT, a 7 French sheath is placed. 5–10 mg of rt-PA is dissolved in 50–100 ml NS. The powerpulse mode of the mainframe AngioJet device is used to pulse-spray the drug into the thrombus during slow advancement and removal of an AngioJet Solent Proxi catheter. The drug is allowed to dwell within the thrombus for 20–30 minutes, then the AngioJet is used in aspiration mode to clear the softened thrombus.

When inflow is limited due to popliteal vein thrombosis, the additional device manipulation and procedure time may increase the chance of re-thrombosis. As such, when treatment is provided in this setting, some consideration should be given to retrograde (downward) delivery of thrombolytic drug into the thrombus below the access site, either by infusing through a sheath with sideholes low in the popliteal vein or by injecting thrombolytic drug into the sheath with an occlusion balloon inflated in the vein just above the sheath to ensure retrograde passage. This can be done either at the initial session or at the first follow-up session. If adequate flow is not restored, infusion CDT may then be performed as described above.

Finally, when stenosis is present (and sometimes for residual thrombus), balloon angioplasty can be used to expand the vein lumen but stent placement is a much less desirable (and probably less effective) option in the femoral vein in the acute DVT setting (6). From an expectations standpoint, we have also found that when an initial balloon inflation in the popliteal vein improves flow but leaves an imperfect appearance, subsequent inflations usually do not result in further improvement and can sometimes provoke acute thrombus formation. Therefore, if further thrombolysis is not favored, it may be best to just leave some residual thrombus with the hope that subsequent anticoagulation will enable further recanalization post-procedure.

Clinical Follow-Up

Patients must receive diligent follow-up care during the initial post-procedure weeks, with particular emphasis on ensuring that anticoagulant therapy is fully therapeutic. Catheter manipulations create endothelial trauma which is a potent pro-coagulant factor. Partly for this reason, and partly due to pre-treatment patient selection bias, re-thrombosis rates after CDT have been surprisingly high in published studies of real-world patient cohorts (7). No studies have compared different anticoagulant strategies in the early weeks after CDT. The traditional route of heparin-based therapy (i.e. unfractionated heparin or low molecular weight heparin (LMWH)) transitioned to warfarin has been time-tested. That said, to have greater confidence that patients are continuously therapeutic during the period of highest risk soon after CDT, we often leave CDT recipients on LMWH for a longer period of time (several weeks) before converting them to warfarin. This decision is often influenced by other factors including the quality of the anatomic result obtained. Other options include fondaparinux or rivaroxaban, which was approved by the FDA in 2012 for the treatment of venous thromboembolism (20). Advantages of rivaroxaban include oral delivery, lack of need for blood monitoring or antecedent heparin, lack of need for dietary modifications, and paucity of drug-drug interactions (unlike warfarin). Disadvantages include the lack of a validated antidote to use should bleeding occur, the inability to determine whether the patient was truly fully therapeutic at any point in time, the rapidity with which loss of anticoagulant effect occurs when doses are missed (compared with warfarin which takes several days to wear off), and the contraindication to use in patients with severe renal disease.

The use of elastic compression stockings (ECS) in patients with proximal DVT was for long thought to prevent PTS based on two single-center, open-label RCTs (21,22). However, the recently completed SOX Trial, a much larger, double-blind, multicenter, North American, placebo-controlled RCT of 806 patients, found ECS to be ineffective in preventing PTS (23). Therefore, while ECS may have a role in helping to manage symptoms of DVT and PTS, the expectation that their use will help to prevent PTS is not supported by the best available data.

Conclusion

The use of endovascular thrombolytic therapy to treat infrainguinal DVT is poorly supported by the available literature but may be worth considering for carefully selected, highly

symptomatic, motivated, younger patients with DVT involving the upper half of the femoral vein who have not improved after 5 days of initial anticoagulant therapy and who are felt to be at substantial risk for PTS and at very low risk for procedural complications. This article summarizes practices that may help to obtain optimal clinical outcomes for these patients.

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Figure 1.

A) Venography via popliteal vein access in a 40 year-old man who developed acute left calf pain and swelling 10 days ago that have worsened despite anticoagulant therapy. There are central filling defects throughout the left femoral vein, consistent with acute DVT. **B)** After overnight catheter-directed thrombolysis with rt-PA at 1.0 mg/hr, there is partial resolution of the thrombus. **C)** Balloon maceration of residual thrombus was performed after rheolytic thrombectomy, resulting in patency of the **D and E)** femoral, common femoral, and iliac veins.

Figure 2.

Anatomic scenarios that may be well-suited for single-session PCDT include partly or completely open below-knee popliteal vein with: **A)** thrombus-free tibial veins; or **B)** thrombus-containing tibial vein(s) but with a popliteal vein “skip segment” that permits inflow from other tibial tributaries.