Catheter-Directed Thrombolysis of Extensive Deep Venous Thrombosis

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The article by Gottlieb[1] in this issue of JLGH offers an excellent overview of the medical therapy of venous thromboembolism. Anticoagulant therapy is, and will remain, the mainstay of treatment for this disease. It is important to remember, however, that anticoagulants do not "cure" deep venous thrombosis (DVT). Rather, they prevent new clot from forming and allow the body's own fibrinolytic system to dissolve the clot and restore venous patency and function. Most of the time, this works well.

For a significant minority of patients, especially those with large burdens of clot, or those whose thrombus begins in the ilio-femoral system and propagates retrograde down the leg, this intrinsic sequence of events may not be enough to prevent long-term complications of DVT. It is well recognized that failure of clot lysis can lead to substantial long-term disability, the so-called *post-thrombotic syndrome* (PTS).[2] This entity occurs for two reasons: a) failure of veins, especially the large veins of the thigh and pelvis, to recanalize; and b) destruction of the slender venous valves with resultant stasis of blood in the lower extremities while in the upright position. Together, these factors lead to chronic venous hypertension and the symptoms of PTS.

PTS usually presents with chronic swelling and pain in the affected extremity, and can progress to skin ulceration and even limb loss. Even without the more dire outcomes of PTS, numerous studies have shown significant cost and disability in the large number of patients affected by this syndrome. In addition, rare patients may present with arterial insufficiency from the intense swelling associated with acute venous thrombosis, so-called phlegmasia cerulea dolens. This represents a medical emergency and represents another indication for more aggressive treatment.

An obvious approach to improve outcomes in DVT is to use agents which actively dissolve clot rather than inhibit its formation. In the 1970's, early thrombolytic agents such as urokinase and streptokinase were tried in an attempt to accelerate clot dissolution and improve results of therapy. While these agents did lead to faster and more complete clot lysis, treatment required such large systemic doses of these drugs, and complications of significant bleeding were sp common, that overall outcomes were not improved. One reason is that systemic drug delivery put very little of the lytic agent where it needed to be, in the clot.

In 1994, a seminal article by Semba and Dake proposed placing a catheter directly into the clotted veins and infusing a thrombolytic agent.[3] In this approach, catheters with multiple sideholes were directed into the clotted veins either from a direct puncture of the popliteal vein or from the jugular approach. Urokinase (no longer available) was then infused into the thrombus over a period of hours or sometimes days, until lysis was achieved. An underlying cause, such as a venous stenosis, was often found, and it could be dilated and stented. These authors documented marked improvement in a small group of patients, and showed at follow-up that the veins remained patent with functioning valves, and that the patients were free of PTS.

Subsequently, a large number of patients have been treated with this approach, and a large multi-center registry has reported favorable results.[4] In 1999, urokinase was taken off the market, which forced practitioners to use alternate lytic agents such as tissue plasminogen activator (tPA). Though tPA is now the most widely used lytic agent, it must be recognized that this is an off-label use of this drug. Indeed, there are not now and never have been any thrombolytic agents approved for catheter-based injection in any vascular system, despite their widespread use in this manner for over 20 years.

We have utilized catheter–directed thrombolysis at LGH since the late 1990's, with generally favorable results. (Figs. 1 & 2) Patient selection is key. Patients with limited clot burden do not justify the risks and expense of

Figure 1: Extensive clot in the femoral vein in a young patient with severe pain and swelling in the affected limb. This clot extended to the common iliac vein in the pelvis.

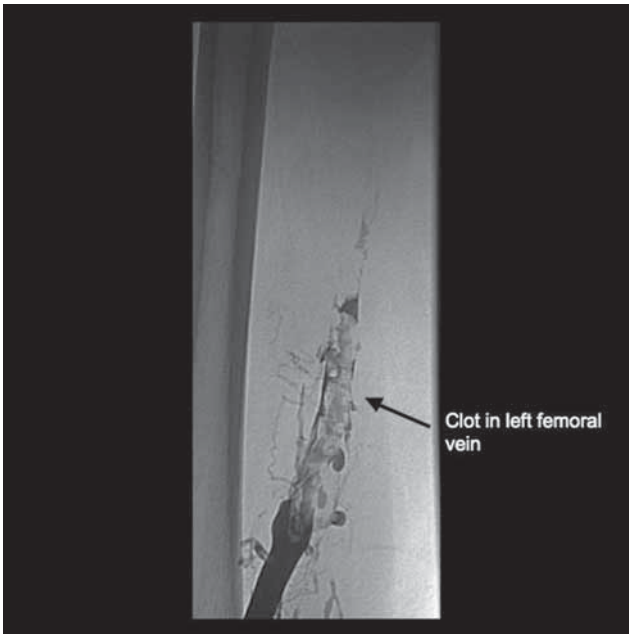


Figure 2: After an overnight infusion of tPA, all clot has been lysed and brisk flow re-established. Note duplication of the femoral vein, a common variant.

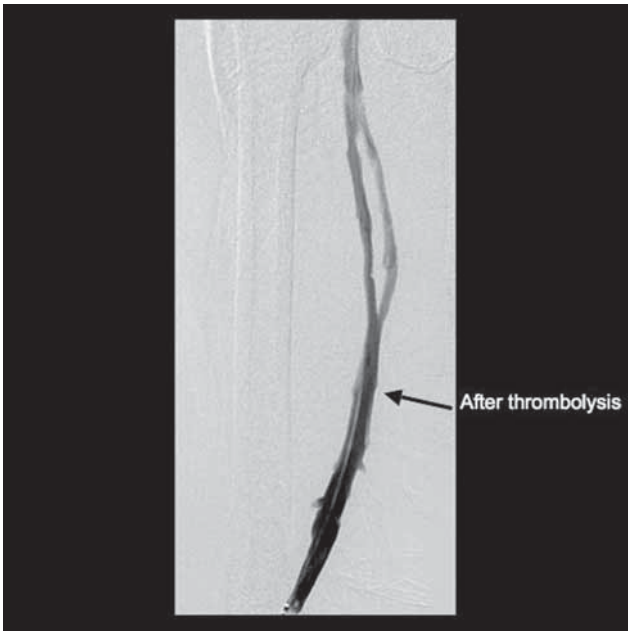


Figure 3: High grade stenosis of the left common iliac vein as it joins the inferior vena cava. This is often caused by chronic venous injury produced by pulsation of the right common iliac artery, which crosses over the vein at this location. This is known as May-Thurner syndrome.

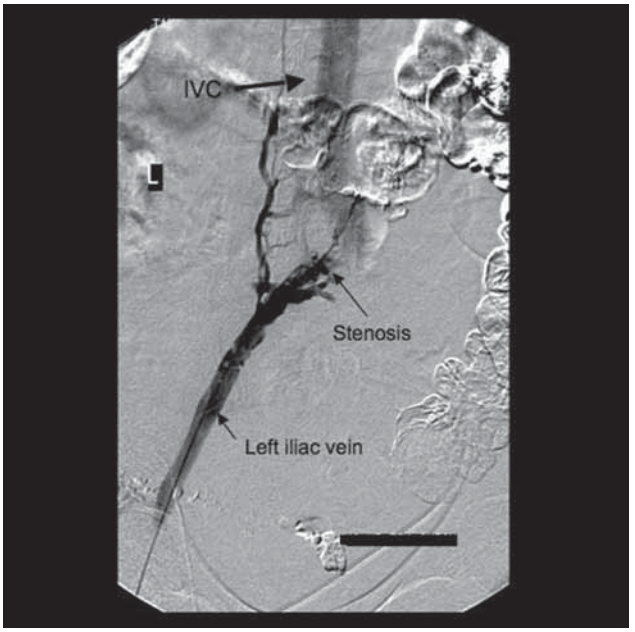
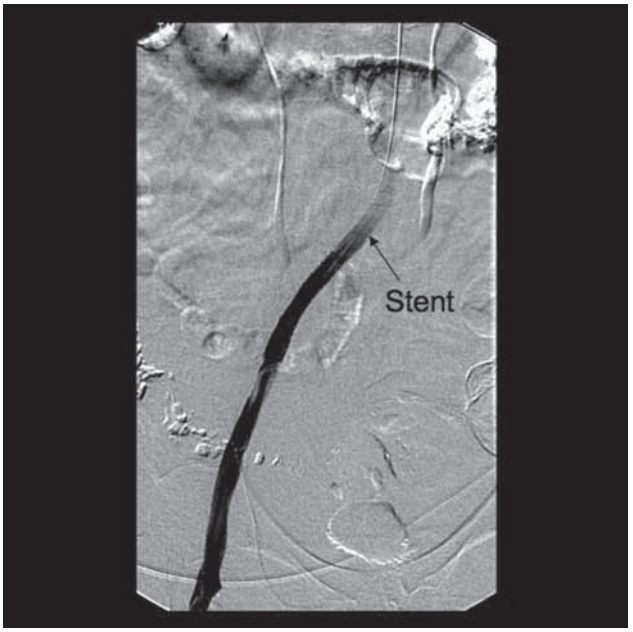
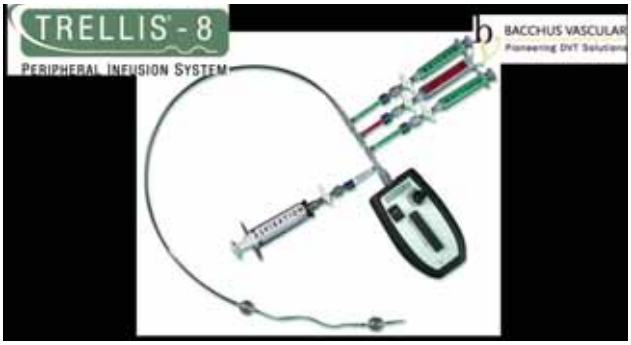


Figure 4: Stent placed at site of stenosis described in Figure 3.



this form of treatment. Nor do the many patients with extensive DVT in association with late-stage cancer, who generally do not live long enough to benefit from a reduced incidence of PTS. Most patients we treat are young to middle-aged patients who present with severe pain and swelling, and are found to have iliofemoral thrombus on ultrasound. A variety of causes may have led to DVT, including:

Figure 5: Trellis-8 Device (see text).



- hypercoagulable states;
- venous stenosis (especially of the upper left common iliac vein-May-Thurner syndrome – Figs. 3 & 4);
- traumatic injury to the vein, often at the groin.

In numerous other cases, no underlying pathology is ever identified. These patients, many of whom are physically quite active, are those most likely to suffer disability from PTS. Therapy need not be started emergently; patients whose clot is a week old have results equal to those with fresher clot. Beyond 3 weeks, however, good outcomes become less frequent.

As in all forms of treatment, there are risk and limitations. Despite the local infusion of tPA, there are still systemic effects. Significant bleeding, usual at the puncture site, but rarely at more critical locations such as brain or GI tract, has been reported in 5-10% of cases. Contraindications to this form of therapy include, among others:

- recent surgery;
- recent stroke;
- history of GI or GU bleeding;
- known vascular malformations in the brain or elsewhere;
- bleeding diatheses.

The infusion requires monitoring in an ICU setting, with frequent trips to the imaging suite to check progress. Venous clot is frequently much slower to lyse than arterial clot, and infusions of 2 or 3 days have been common. All of this leads to significant expense and discomfort for the patient, which has in turn, discouraged more widespread use of this form of treatment for patients with more limited clot burden.

These limitations have been partially addressed by several new approaches, which we have been using. Cynamon et al. reported the use the Angiojet device (Possis Medical) to forcefully inject a solution of tPA into venous clot over a short period of time, dubbed the "Power Pulse Spray" technique.[5] After waiting 20-30 minutes, the liquefied clot is then aspirated. Any remaining clot can then be treated with a shorter infusion of tPA to restore full patency. We have treated a small number of patients with this technique. Results have been generally favorable, and treatment times have usually been under 24 hours from start to finish. More recently, the Trellis-8 Device (BacchusVascular)[6] has become available. (Fig. 5) This catheter isolates a segment of thrombosed vein, injects thrombolytic agent directly into the clot, and the "stirs" the clot and lytic agent together with a rotating wire that acts like a blender. The clot is then aspirated, the catheter moved to a new segment, and the process repeated. A recent paper[6] has documented a significant increase in success, dramatically shorter treatment times, and reduced cost when compared to conventional catheter-directed techniques. We have treated several patients with this device and have had uniformly good results.

There is a distinct need for a large, multi-center trial to firmly establish the validity of catheter-directed thrombolysis, to clearly show which patients are best treated with this approach, and to demonstrate the optimal technique for safe and cost-effective therapy. In the meantime, we will continue to apply this technique to selected patients most likely to be disabled by PTS or with limbs threatened by the severity of thrombosis.

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