VENOUS THROMBOLYSIS

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Introduction

Endovascular thrombolytic techniques can be invaluable in managing patients with venous thrombosis. However, the wide range of thrombolytic techniques offered can be confusing to the individual practitioner who would like to add these treatments to his/her repertoire. The purpose of this document is to provide a straightforward approach to patient selection, procedure performance, and post-procedure monitoring that can be easily adopted by interventional radiologists starting to perform venous thrombolysis.

Patient Selection

At present, there are no published randomized clinical trials that guide clinical practice regarding the proper indications for Endovascular Thrombolysis in the treatment of DVT. However, significant progress has been made in recent years towards harmonizing the clinical practice guidelines of different subspecialists. Most notably, in 2008, the practice guidelines of the Society of Interventional Radiology (SIR) and the American College of Chest Physicians (ACCP) finally came into consensus on this issue (1,2). In general, an individualized approach to patient selection should be used, taking into account the anatomic extent of thrombosis, symptom duration/severity, the patient's likelihood of developing the post-thrombotic syndrome (PTS), and the patient's likelihood of having a bleeding complication. Absolute contraindications to therapy include active internal bleeding, disseminated intravascular coagulation, recent (< 3 months) cerebrovascular event, recent central nervous system surgery/trauma, and any absolute contraindication to anticoagulation. Strong relative complications include recent CPR, major surgery, delivery, biopsy, trauma, eye surgery, or bleeding event, other intracranial lesion or disorder, uncontrolled hypertension, thrombocytopenia, known right-to-left cardiopulmonary shunt, renal failure, pregnancy, severe hepatic dysfunction, septic thrombophlebitis, and diabetic hemorrhagic retinopathy.

A. Lower Extremity DVT:

A multicenter registry and vast clinical experience have shown that Endovascular Thrombolysis is more effective in removing acute thrombus compared with chronic organized thrombus (3). There are three primary reasons to perform Endovascular Thrombolysis in patients with acute DVT: 1) to prevent major immediate clinical sequelae such as death, limb loss, pulmonary embolism, and renal failure in patients with phlegmasia cerulea dolens or IVC thrombosis; 2) to alleviate severe or incapacitating DVT symptoms in patients with extensive proximal DVT; and 3) to prevent post-thrombotic syndrome (PTS) as a first-line treatment for patients with acute proximal lower extremity DVT. Because the ability of Endovascular Thrombolysis to prevent PTS has not been definitively established, patients treated with the primary goal of PTS prevention should be informed of the long-term risks of PTS; the risks, benefits, and alternatives to thrombolysis; and the lack of conclusive evidence in favor of (or against) its ability to prevent PTS.

Poor candidates for Endovascular Thrombolysis include patients with bleeding predisposition, patients who do not ambulate at baseline or who have poor life-expectancy (less benefit from PTS prevention), and patients with chronic femoropopliteal DVT (Endovascular Thrombolysis is much less effective) (3) isolated calf DVT (PTS rates are probably lower), or asymptomatic DVT (PTS is rare). Patients with acute iliofemoral DVT appear to be the best candidates for therapy - they are at higher baseline risk of PTS and Endovascular Thrombolysis has shown strong potential to prevent PTS and improve QOL (4-6).

B. Upper Extremity DVT:

PTS of the upper extremity, particularly when within the dominant arm, can also impair QOL (7). For this reason, patients with acute axillosubclavian DVT may also be candidates for Endovascular Thrombolysis. In general, the etiology of thrombosis plays a key role in determining optimal therapy.

Primary axillosubclavian vein thrombosis typically occurs in association with compression of the subclavian vein from surrounding ligamentous and muscular structures in the thoracic outlet. For these patients, who are often young and otherwise healthy, modern treatment features a combined interventional-surgical approach: Endovascular Thrombolysis to eliminate the acute thrombus, followed by surgical thoracic outlet decompression with or without direct venous repair/bypass to prevent recurrence. Aggressive angioplasty and stent placement are not performed in order to avoid further traumatizing the subclavian vein, and because stents tend to fracture in this location.

Treatment of patients with **secondary** axillosubclavian venous thrombosis is dependent upon the degree of symptoms and overall patient condition. In general, symptomatic younger patients without major co-morbidities that would elevate bleeding risk are candidates for Endovascular Thrombolysis. Because many such cases are related to stenosis caused by prior central venous catheters and other devices, balloon angioplasty often plays a major role in treatment as well.

Procedural Technique

A number of image-guided clot removal strategies may be employed to treat acute DVT. In this section, the basic procedural technique for administering these treatments is described.

The following is a brief description of the originally described technique for acute DVT, known as Catheter-Directed Intrathrombus Thrombolysis (CDT), originally introduced in the early 1990s (8):

A. Venous Access: Venous access with a micropuncture system should be obtained using real-time ultrasound guidance to avoid inadvertent arterial punctures. When possible, a lower extremity vein should be selected at a site lower than the most distal extent of thrombosis. For many patients with iliofemoral DVT, the popliteal vein provides the best access site; however, patients with thrombus involving the popliteal vein and upper calf veins may be better treated with access into the small saphenous vein or posterior tibial vein. The internal jugular vein is another option.

B. Catheter Venography: Once venous access is obtained, diagnostic venography is performed to accurately define the extent of thrombosis. A 6-8 French sheath is placed.

C. Initiation of Thrombolysis: A multisidehole catheter is embedded within the thrombus and a thrombolytic drug is infused in drip fashion. The patient is simultaneously anticoagulated to subtherapeutic levels using unfractionated heparin. The patient is monitored in an ICU or stepdown unit, and serial laboratory values are obtained every 6-8 hours. The hematocrit and partial thromboplastin time are closely monitored. In some centers, fibrinogen levels are followed as well, although there is no conclusive evidence that this practice prevents adverse events. Many physicians that follow these levels will discontinue the thrombolytic drug when the fibrinogen falls below 100 mg/dl, although there is great variation in this aspect of practice.

D. Follow-Up Checks: At 6-18 hour intervals, repeat venography is performed. One of several findings is seen: a) Complete thrombolysis with no venous stenosis – therapy is deemed successful and the infusion is terminated; b) Complete thrombolysis with a venous stenosis identified – iliac vein stenoses are treated with endovascular stent placement and femoral vein stenoses are treated with balloon angioplasty; c) Incomplete thrombolysis – an angioplasty balloon is used to macerate the thrombus, the infusion catheter is repositioned, and the infusion is continued. If no thrombolysis is seen within 24-48 hours, therapy is discontinued (failure).

Several basic elements of the original CDT procedure have been modified in recent years:

Choice of Thrombolytic Drug and Delivery Catheter: To date, no studies have demonstrated differences in safety or efficacy between different thrombolytic drugs using current dosing regimens (9,10). Regarding delivery catheters, a multisidehole catheter is the standard way to achieve intrathrombus drug delivery. A new approach is the use of ultrasound energy to loosen fibrin strands and better disperse the thrombolytic drug – an ultrasound-assisted thrombolytic infusion catheter (EKOS, Bothell, WA) is now available for this purpose. The theoretical advantage of this approach is that it may allow optimal dispersion of the drug within the clot without resorting to mechanical manipulation that may traumatize the vein wall/valves.

The following regimens are considered acceptable dosing schemes for traditional infusion-first CDT of DVT. Of note, none of the drugs described has an FDA indication for DVT treatment.

1. Urokinase: 120,000 – 180,000 units/hr – Dissolve 1 million units UK in 500 ml normal saline (= 2000 units/ml). Infuse at 60-90 ml/hr.

2. Tissue Plasminogen Activator: 0.01 mg/kg/hr, which usually corresponds to 0.5 – 1.0 mg/hr – Dissolve 10 units TPA in 1000 ml normal saline (= 0.01 mg/ml). Infuse at 50-100 ml/hr.

3. Reteplase: 0.25 – 0.50 units/hr – Dissolve 10 units reteplase in 1000 ml normal saline (= 0.01 units/ml). Infuse at 25-50 ml/hr.

4. Tenecteplase: 0.25 – 0.5 mg/hr – Dissolve 5 mg TNK in 500 ml normal saline (= 0.01 mg/ml). Infuse at 25-50 ml/hr.

Percutaneous Mechanical Thrombectomy (PMT) and Pharmacomechanical CDT (PCDT): To date, no stand-alone PMT method has been reliably effective in DVT treatment without concomitant use of a fibrinolytic drug. However, the combination of pharmacologic CDT with PMT, known as PCDT, has shown great potential to speed thrombolysis, reduce the required drug dose, and reduce complications (11). Several different PCDT methods have been used: a) Thrombolytic drug infusion (CDT) followed by PMT to macerate or remove thrombus; b) Initial PMT with an aspirating-type device to debulk the thrombus and create a flow channel, followed by CDT (12); and c) Recently two pharmacomechanical techniques have been introduced to enable on-table, single session DVT treatment (see below) (13,14).

Single-Session PCDT techniques involve the delivery and rapid dispersion of a significant dose of the thrombolytic drug as the first step in thrombus removal. Typically, 5-25 mg of rt-PA (or the equivalent) is administered during the initial session. Different devices rely upon different methods to achieve rapid drug dispersion within the thrombus. Two commonly used techniques are described below.

A. PowerPulse Thrombolysis (13) using the AngioJet Rheolytic Thrombectomy System (Possis Medical, Minneapolis, MN): Typically 5-20 mg of TPA (or the equivalent) is dissolved in 50-100 ml normal saline. An AngioJet Xpeedior or DVX catheter is advanced to and fro within the thrombus over a guidewire during device activation with its outflow port occluded with a stopcock (15). This results in powerful pulse-spray delivery of the thrombolytic drug solution into the clot. After a dwell period of 20-30 minutes, the AngioJet is used in aspiration mode to remove any softened residual clot.

B. Isolated Thrombolysis (14) using the Trellis Peripheral Infusion System (Bacchus Vascular, Santa Clara, CA): A Trellis catheter is advanced over a guidewire to the cephalad extent of the thrombus.

Two balloons mounted on the Trellis catheter are first inflated to “isolate” the thrombosed venous segment. The thrombolytic drug (usually 4-8 mg TPA or the equivalent), diluted to 10 ml, is injected via a syringe into the catheter in small aliquots over a 10 minute period and enters the thrombus through several sideholes. A sinusoidal wire oscillates within the catheter (many physicians use run times of 10 minutes) to mechanically macerate the thrombus and disperse the drug. The liquefied thrombus and drug may then be aspirated through a sideport in the catheter, and the catheter is re-positioned within any remaining thrombus and the above steps repeated if needed.

Because Single-Session PCDT may be more mechanically aggressive than Infusion-First CDT, most physicians anticoagulate the patient to therapeutic levels during PCDT. After the initial PDCT treatment, patients are evaluated venographically and balloon maceration, aspiration thrombectomy, and/or PMT used to remove residual thrombus. After a repeat venogram, a decision is made as to whether infusion CDT will be needed to clean up residual thrombus. Adjunctive therapy using balloon angioplasty and/or stent placement is performed as described above.

Post-Procedure Care

It is very important for the interventional radiologist to be able to manage the transition from Endovascular Thrombolysis to long-term DVT management, and to educate the patient’s primary care physician on those aspects of DVT care relevant to the IR’s experience. First, patients must transitioned to long-term anticoagulant therapy. He/she may ambulate within several hours after sheath removal (assuming a lower extremity access site) and can usually be discharged from the hospital 4-24 hours afterwards unless there are other medical issues. Typically patients are placed on oral warfarin and are given low-molecular weight heparin during the transition period – this is discontinued when the patient reaches the desired therapeutic range (INR 2.0 – 3.0). During this transition period, the interventionalist should ensure that appropriate INR monitoring is conducted and warfarin doses adjusted accordingly. Second, patients typically undergo risk factor evaluation to determine the appropriate duration of anticoagulant therapy – this may be done with hematology consultation in many instances. In general, patients with time-limited major reversible risk factors only (i.e. major surgery or trauma with no other risk factors) receive at least 3 months of therapy while those with unprovoked DVT receive longer durations (1). Third, patients with lower extremity DVT should be asked to wear a Class II (30-40 mmHg) graduated compression stocking to the affected limb for prevention of PTS – two single-center randomized trials have shown that this intervention may decrease PTS rates by 50% (15,16). Fourth, patients and their physicians should be educated about the need to inform the interventionalist should symptoms recur, since re-stenosis can sometimes be treated with repeat balloon angioplasty or stent placement before re-thrombosis occurs. Fifth, routine clinical follow-up with the interventionalist should ideally be arranged.

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