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Outcomes and predictors of failure of thrombolysis for iliofemoral deep venous thrombosis

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Background: **Catheter-directed thrombolysis (CDT) with adjunctive mechanical techniques, when successful, is reported to alleviate symptoms of acute iliofemoral deep venous thrombosis (IFDVT) and to lower the occurrence of the post-thrombotic syndrome (PTS). This study aimed to determine longer term outcomes of catheter-based interventions for IFDVT and to identify predictors of immediate and mid-long-term failures that would guide optimal patient selection.**

Methods: **Consecutive patients who underwent CDT or pharmacomechanical thrombolysis for IFDVT between May 2007 and March 2013 were identified from a prospectively maintained database. Assessment of predictors of immediate periprocedural failure was based on the degree of clot lysis (≤50% vs >50%) and 30-day recurrence of DVT. Long-term anatomic and clinical failures and outcomes were assessed by ultrasound imaging of the lysed segments and Villalta score (≥5 vs <5). Survival analysis was used to assess primary patency and PTS morbidity. Multivariate binary logistic and Cox regression models were used to determine predictors of anatomic and clinical failures.**

Results: **During the study period, 93 patients (118 limbs; mean age, 49.4 ± 16.2 years; 47 women) with symptoms averaging 11.1 ± 9.6 days in duration were treated with various combinations of CDT or pharmacomechanical thrombolysis; in 52 (56%), at least one iliocaval stent was deployed. Immediate treatment failure was seen in 11 patients (12%) predicted by the preoperative indication "phlegmasia" (odds ratio, 3.12; $P = .042$) and recent surgery (odds ratio, 19.6; $P = .018$). At a mean ultrasonographic follow-up of 16 ± 14 months (range, 1-65 months), six more patients sustained a rethrombosis, accounting for an overall 3-year primary patency of 72.1%. In the long-term model, loss of primary patency was associated with recent surgery (hazard ratio [HR], 4.04; $P = .023$), malignant disease (HR, 6.75; $P = .016$), and incomplete thrombolysis (≤50%) (HR, 5.83; $P < .001$). By stratification of PTS on the basis of postprocedure failures, at 2 years PTS occurred in 50.6% of patients and in 16.3% of patients without failure ($P < .001$).**

Conclusions: **Thrombolysis for symptomatic IFDVT can achieve high rates of thrombus resolution and reduce long-term PTS morbidity on careful patient selection. Improved anatomic and clinical outcomes are associated with the completeness of thrombolysis. (J Vasc Surg: Venous and Lym Dis 2015;3:35-41.)**

Catheter-directed thrombolysis (CDT) and pharmacomechanical thrombolysis (PMT), alone or combined, are increasingly employed for the treatment of selected patients with acute iliofemoral deep venous thrombosis (IFDVT), targeting early thrombus removal, maintenance of valvular competence, and post-thrombotic morbidity reduction.[1,2] Despite the described benefits of catheter-based interventions for IFDVT in various trials, the results have been inconsistent.[3-5] Thus the societal guidelines put forward have mixed recommendations. The most recent guidelines of the American College of Chest Physicians recommend anticoagulation alone vs CDT, whereas the Society of Interventional Radiology and the Society for Vascular Surgery suggest CDT or PMT in select patients.[6-8] Subsequently, CDT and PMT may not be considered first-line therapy. Recently, the Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis (CaVenT) randomized study reported that additional CDT should be considered as first-line therapy in patients with proximal DVT and low risk of bleeding.[9]

There is little doubt that the overall benefit of thrombolysis depends on multiple factors, including predisposing risks, symptom duration, thrombus extension, and technical approaches and interventional success. The identification of patients who will achieve favorable outcomes and derive long-term benefits from intervention is therefore paramount. This study aimed to define predictors of immediate and mid-long-term anatomic and clinical failures to guide patient selection and to set a standard for patient and physician expectations.

METHODS

The study protocol was reviewed and approved by the Institutional Review Board of the University of Pittsburgh. No study specific consent was required as no patient identifiers were collected and the study received an exempt status. All patients gave informed consent to undergo the procedures listed.

Study design. Consecutive patients who underwent CDT or PMT for IFDVT between May 2007 and March

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2013 were identified from a prospectively maintained database. Patient records were reviewed for demographics, baseline risk factors, lower extremity venous studies, indications, intraprocedural data, periprocedural complications, and long-term outcomes. The end points were immediate treatment failure, long-term vessel patency based on ultrasonography of the lysed segments, and occurrence of the post-thrombotic syndrome (PTS).

Definitions. Our indications to offer thrombolysis as an alternative to anticoagulation alone were restricted to symptomatic patients with IFDVT and no absolute contraindication to lysis as recommended by the Society for Vascular Surgery guidelines.[8]

Immediate treatment failure was defined as clot lysis ≤50% or 30-day DVT recurrence.[10] The rate of clot lysis was estimated on the basis of the amount of residual clot at the completion venogram compared with the pretreatment venogram as previously described.[10] The physicians interpreting the phlebograms (E.D.A., A.N.) were blinded to the clinical outcomes of the patients.

PTS was assessed according to the Villalta score. The Villalta score is based on five patient-related venous symptoms (pain, cramps, heaviness, paresthesia, and pruritus) and six clinician-assessed physical signs (pretibial edema, skin induration, hyperpigmentation, venous ectasia, redness, and pain during calf compression), which are rated on a 4-point scale: 0, none; 1, mild; 2, moderate; and 3, severe. Points are calculated with a total score ranging between 0 and 33. Patients were classified as having PTS if their score was ≥5.

A major complication was defined as any event that required interventional treatment, rehospitalization, or persisting kidney function deterioration within 30 days of the procedure.

Freedom from rethrombosis was defined as continued patency of the iliofemoral or caval segment that was treated, irrespective of the popliteal or distal vein segments.

Periprocedural protocol. Patients were administered intravenous heparin before the procedure based on a DVT protocol to maintain therapeutic partial thromboplastin times. All patients underwent duplex ultrasound imaging before the intervention. In addition, the majority of patients were also evaluated with computed tomography venography of the abdomen and pelvis with intravenous administration of contrast material. All interventions were performed by vascular surgeons in endovascular suites equipped with fixed imaging capability (GE Healthcare, Chalfont St Giles, United Kingdom). All patients were discharged with therapeutic oral anticoagulation or low-molecular-weight heparin, with graduated elastic compression stockings (20-30 mm Hg). The duration of anticoagulation was determined on the basis of the underlying cause and the presence of a hypercoagulable state as recommended in the American College of Chest Physicians guidelines.[6] Although these were the goals and recommendations relayed to patients on discharge and future follow-up, this was limited by patient compliance and socioeconomic factors. Antiplatelet therapy with aspirin was initiated in patients who received an iliac vein stent.

Thrombolysis technique. Our technique has been thoroughly described elsewhere.[11-14] All patients were treated under conscious sedation and local anesthesia. Use of temporary inferior vena cava filters was routine early in our experience out of concern for pulmonary embolism and based on the physician's preference, but it has since become more selective. Ultrasound-guided popliteal vein access was used in the majority of patients (prone position) regardless of whether the clot involved the popliteal or tibial veins. Unfractionated intravenous heparin was routinely administered (100 U/kg). Ascending venography was performed through a 6F or 8F sheath. In patients with thrombosis at the popliteal access site, 2 mg of tissue plasminogen activator (tPA, Alteplase; Genentech, San Francisco, Calif) was delivered through the sheath at the beginning of the procedure. In patients with acute DVT (<14 days), PMT was used with the intent of providing a single-session treatment, if possible. PMT was performed with either the AngioJet catheter (Bayer Healthcare, Medrad Inc, Indianola, Pa) or the Trellis device (Covidien Vascular, Mansfield, Mass). Device use was at the discretion of the operator. With the AngioJet catheter, the power-pulse mode was used initially, administering 6 to 8 mg of tPA into the thrombus. The catheter was then reactivated in thrombectomy mode after a dwell time of 10 to 15 minutes. Similar doses of tPA were administered with the Trellis device for each 30-cm segment treated. Catheter-directed lysis was used sparingly, either as a primary or as a secondary intervention with a multi-sidehole catheter. This was reserved for residual thrombus after PMT, for patients with subacute DVT (>14 days old), or for those in whom the age of the clot was ill-defined. In addition, ultrasound-assisted lysis with the EKOS catheter (EKOS Corporation, Bothell, Wash) was occasionally used as an initial therapy at the discretion of the operator. Typically, patients undergoing thrombolysis in multiple sessions were brought back to the angiography suite for scheduled lysis checks at 12- to 24-hour intervals. Iliac vein stenosis seen on completion venography was routinely treated with self-expanding stents (Wallstent, Boston Scientific, Natick, Mass; or Protégé, Covidien, Plymouth, Minn). The common iliac vein was typically stented with a 14- to 16-mm stent, and the external iliac vein was typically stented with a 12- to 14-mm stent. The length chosen was tailored to cover the diseased segment. All patients continued systemic anticoagulation after the lysis intervention. Filter retrieval was either performed at the completion of the lysis procedure or scheduled for a later date on the basis of the presence of residual thrombus because of its perceived risk of embolization.

Follow-up. Duplex ultrasound imaging was performed to assess for vessel patency and to evaluate for venous reflux and valvular competence. Reflux was determined at the femoral and popliteal levels and was considered significant if >1 second. Additional imaging (venography, computed tomography venography, or magnetic resonance venography) was performed for clinically