Deep Venous Thrombosis: An Interventionalist’s Approach

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ABSTRACT

Background: Deep venous thrombosis (DVT) of the lower extremity has traditionally been anatomically categorized into proximal DVT (thrombosis involving the popliteal vein and above) and distal DVT (isolated calf vein thrombosis). Proximal DVT involving the common femoral and/or iliac veins, referred to as iliofemoral DVT (IFDVT), represents a disease process with a worse prognosis and higher risk for poor clinical outcomes compared to proximal DVT not involving the common femoral or iliac draining veins.

Methods: This review discusses therapeutic options for treatment of lower extremity IFDVT, including adjuvant anticoagulation and catheter-based invasive therapies; literature supporting current acute interventional techniques; and the recommendations from the recently published American Heart Association guidelines.

Results: Patients with IFDVT represent an opportune subset of patients for acute interventional management with currently available techniques. This subset of patients with proximal DVT has a worse prognosis, is less well studied, and benefits more from acute intervention compared to patients with proximal DVT or distal DVT.

Conclusion: Invasive catheter-based therapies that remove thrombus and correct venous outflow obstructions improve outcomes and morbidity in patients with IFDVT. Future trials that address IFDVT specifically will improve our understanding and the proper management of this higher-risk subset of patients with DVT.

INTRODUCTION

Venous thromboembolism is responsible for >250,000 hospital admissions per year and is a major cause of morbidity and mortality in the United States. Despite the astounding number of affected patients, published guidelines have only recently addressed invasive therapies for the treatment of iliofemoral deep venous thrombosis (IFDVT).1,2 Previously published guidelines from the American College of Chest Physicians and the European Society of Cardiology (ESC) focus on acute and chronic medical therapies for venous thromboembolism but do not provide information to guide the use of more aggressive, invasive, catheter-based therapies and thrombolysis options that have shown promising outcomes for the treatment of IFDVT.3,4

Historically, the anatomic division of lower extremity deep venous thrombosis (DVT) has been either proximal DVT (involving the popliteal vein and proximal veins) or distal DVT (involving a calf vein and distal veins) because of the increased risk of pulmonary embolism in patients with proximal DVT. This division is appropriate for clinical purposes because a more extensive proximal thrombus burden translates into worse patient outcomes. For the purpose of catheter-based management of lower extremity DVT, however, an anatomic division at the level of the iliofemoral veins is more appropriate. The venous drainage of the lower extremity depends on the patency of the iliofemoral veins; an understanding of this anatomy is necessary to properly treat IFDVT (Figure 1).

Thrombus is present in the common femoral vein and/or iliac vein in 25% of symptomatic patients with lower extremity DVT.5 Thrombus present in one or both of these veins defines IFDVT irrespective of thrombus involvement in veins above the iliac vein or...
below the common femoral vein. Thrombotic occlusion of the iliofemoral veins not only occludes the primary anatomic route for venous outflow of the lower extremity but also occludes the only collateral route for venous drainage of the lower extremity. Clinically, venous obstruction of the iliofemoral veins translates into severe symptoms of DVT and an increased incidence of late clinical sequelae and postthrombotic syndrome (PTS). Common symptoms of PTS include venous ulcers, venous claudication, physiological abnormalities, and impaired quality of life.

The prognosis for patients with IFDVT is worse than the prognosis for patients with proximal DVT because of the anatomic differences mentioned above. Two prospective cohort studies demonstrated that patients with symptomatic IFDVT have increased rates of complications, including more than a 2-fold increase in PTS during a 2-year follow-up period and a 2.4-fold increase in the risk of recurrent venous thromboembolism during a 3-month follow-up period compared to patients with proximal DVT. The recent push for a more aggressive interventional approach in the subset of patients with IFDVT is supported by the increased morbidity and prevalence of PTS in this population of patients. This review discusses the current management of patients with IFDVT from initial anticoagulation to interventional therapy to long-term guideline-supported treatment.

INITIAL ANTICOAGULATION

The recommended therapy for patients presenting with IFDVT is intravenous (IV) or subcutaneous anticoagulants to prevent recurrent DVT and pulmonary embolism. Evidence to support this practice is extrapolated from recommendations of the American Heart Association (AHA) and the ESC for the larger population of patients with proximal DVT. The recommended initial anticoagulation dosages (Table 1) for patients presenting with IFDVT are the same as those for patients presenting with proximal DVT: (1) IV unfractionated heparin bolus of 80 units/kg followed by a continuous infusion of 18 units/kg/hr for 5-7 days; (2) subcutaneous low molecular weight heparin with enoxaparin 1 mg/kg twice daily or 1.5 mg/kg once daily, dalteparin once daily at 200

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Dosage</th>
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<tr>
<td>Unfractionated heparin</td>
<td>80 U/kg bolus followed by a continuous infusion of 18 U/kg/hr for 5-7 days</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1 mg/kg twice daily or 1.5 mg/kg once daily</td>
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<tr>
<td>Dalteparin</td>
<td>100 IU/kg twice daily</td>
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<tr>
<td>Dalteparin</td>
<td>200 IU/kg once daily</td>
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<tr>
<td>Tinzaparin</td>
<td>175 anti-Xa IU/kg once daily</td>
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<tr>
<td>Fondaparinux</td>
<td>5 mg daily, body weight &lt;50 kg</td>
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<tr>
<td>Dalteparin</td>
<td>7.5 mg daily, body weight 50-100 kg</td>
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<tr>
<td>Dalteparin</td>
<td>10 mg daily, body weight &gt;100 kg</td>
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<tr>
<td>Argatroban</td>
<td>2-10 µg/kg/min infusion</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>0.4 mg/kg bolus, 0.15 mg/kg infusion</td>
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Table 2. Thrombolytic Infusion Dosing

<table>
<thead>
<tr>
<th>Fibrinolytic Drug</th>
<th>Infusion Dose</th>
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<tr>
<td>Streptokinase</td>
<td>100,000 IU/hr infusion</td>
</tr>
<tr>
<td>Urokinase</td>
<td>120,000 to 180,000 U/hr</td>
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<tr>
<td>Alteplase</td>
<td>0.01 mg/kg/hr</td>
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IU/kg or twice daily at 100 IU/kg, or tinzaparin once daily at 175 anti-Xa IU/kg without routine antifactor Xa monitoring; or (3) subcutaneous fondaparinux 5 mg daily for patients <50 kg, 7.5 mg daily for patients 50-100 kg, or 10 mg daily for patients >100 kg. Fixed-dose, weight-adjusted subcutaneous unfractionated heparin could also be considered, although data are more limited for this regimen. Direct thrombin inhibitors may be substituted with either IV argatroban or lepirudin for patients with heparin-induced thrombocytopenia.

SYSTEMIC THROMBOLYSIS

Several randomized controlled trials using systemic thrombolyis for the treatment of proximal DVT have been reported in the literature. Although IFDVT represents a subset of patients in these trials, no literature specifically addresses the use of tissue plasminogen activator (TPA) or streptokinase for the treatment of IFDVT. Systemic thrombolysis for proximal DVT with TPA results in >50% clot lysis more often than heparin alone (58% vs 0%, P=0.002) but does not significantly reduce PTS (25% vs 56%, P=0.07) in patients with successful lysis. A pooled analysis of randomized trials in patients with proximal DVT demonstrated >50% clot lysis significantly more often in patients treated with systemic IV streptokinase than in patients treated with standard unfractionated heparin anticoagulation. The rate of PTS at long-term follow-up was significantly reduced in patients treated with systemic IV streptokinase compared to heparin anticoagulation alone (24% vs 67%, P=0.01) in a small randomized trial of 35 patients. Major bleeding was significantly increased with the use of systemic streptokinase (14% vs 4%, P=0.04) compared to unfractionated heparin alone. These studies did not focus specifically on patients with IFDVT but included all patients with proximal DVT. Moreover, a limitation of the available information is the lack of studies comparing TPA and streptokinase in the treatment of proximal DVT. For these reasons, catheter-directed thrombolysis may represent a more desirable treatment for patients with IFDVT. Dosing for thrombolytic infusion is summarized in Table 2.

ACUTE THROMBUS REMOVAL THERAPIES

The acute and long-term outcomes of DVT are improved with complete removal of venous thrombus. Percutaneous mechanical outcomes of DVT are improved with complete removal of venous thrombus. Percutaneous mechanical thrombectomy and catheter-directed thrombolysis are 2 interventional techniques that acutely remove thrombus in the venous system and can potentially lead to better outcomes. These methods significantly reduce recurrent DVT, valvular reflux, venous obstruction, and PTS. These comorbidities are significantly increased at long-term follow-up in the presence of residual thrombus after routine anticoagulation for DVT. A positive correlation between increased risk of recurrent DVT and residual thrombus after anticoagulation therapy was demonstrated in a metaanalysis of 11 randomized controlled trials. Subgroup analyses from 2 prospective studies demonstrated twice the risk of recurrent venous thromboembolism and PTS if residual thrombus is present on a 6-month follow-up ultrasound. The presence of residual thrombus may be a marker for subsequent thrombus formation or may possibly provide a nidus for new thrombus formation, making complete removal of venous thrombus desirable.

Catheter-Directed Thrombolysis

Catheter-directed thrombolysis is a fluoroscopically guided invasive procedure utilizing an infusion catheter to deliver thrombolytic agents directly into venous thrombus. The increased interest in this technique stems from the ability to facilitate the early removal of thrombus that leads to improved long-term benefits. Percutaneous therapy in the acute phase of venous thrombosis can prevent valvular damage, PTS, and recurrent venous thrombosis. The benefit of catheter-directed thrombolysis to prevent long-term sequelae of DVT outweighs the risk of bleeding complications associated with the use of thrombolytic agents because of the reduced dose possible with this technique. Even though most literature on this topic includes all lower extremity DVT, the subset of IFDVT patients is usually reported separately.

Mewissen et al reported a prospective multicenter registry of 473 patients receiving catheter-directed thrombolysis for the treatment of symptomatic lower extremity DVT with urokinase infusion for a mean of 53 hours in 287 patients for a total of 303 affected limbs and 312 infusions; 221 patients had IFDVT. The study reported >50% lysis in 83% of patients. Although a wide variety of urokinase dosing schemes were utilized, major access-site bleeding occurred in 11% of patients in this registry. Using the same registry as Mewissen, Comerota et al identified 68 patients with IFDVT treated with catheter-directed...
thrombolysis and 30 patients treated with anticoagulation alone to compare health-related quality-of-life questionnaires. The patients who received catheter-directed thrombolysis had fewer postthrombotic symptoms than the patients treated with anticoagulation alone \( (P=0.006) \). \(^{33}\)

Significant long-term symptom resolution using catheter-directed thrombolysis to treat IFDVT has been demonstrated in 2 small studies. A controlled trial by Elsharawy et al randomized 35 patients to either catheter-directed thrombolysis followed by anticoagulation or anticoagulation alone. Six-month patency rates were significantly increased with thrombolysis \( (72\% \text{ vs } 12\%, \ P<0.001) \), and venous reflux was significantly increased in patients treated with anticoagulation alone \( (41\% \text{ vs } 11\%, \ P=0.04) \). \(^{34}\) A prospective nonrandomized study \( (n=51) \) by AbuRahma et al \(^{32}\) demonstrated significant long-term symptom resolution in patients with IFDVT who were treated with catheter-directed thrombolysis and stenting compared to anticoagulation alone \( (78\% \text{ vs } 30\%, \ P=0.0015) \).

Enden et al reported an open-label, multicenter, randomized controlled trial \( (n=118) \) demonstrating improved long-term outcomes in patients with proximal DVT treated with catheter-directed thrombolysis. \(^{35}\) Patency at 6 months was increased with catheter-directed thrombolysis vs anticoagulation alone \( (64\% \text{ vs } 36\%, \ P=0.004) \), and venous obstruction was reduced with catheter-directed thrombolysis vs anticoagulation alone \( (20\% \text{ vs } 49\%, \ P=0.004) \). Femoral venous insufficiency was identical between the 2 groups. In 2% of patients, major bleeding occurred with catheter-directed thrombolysis utilizing recombinant TPA infusions at 0.01 mg/kg/hr, and in 1.7% of patients, major bleeding occurred with anticoagulation alone. \(^{35}\) A pooled analysis of randomized trials using similar doses of thrombolytic agents for catheter-directed thrombolysis reported a 2%-4% incidence of major bleeding complications. \(^{38}\) The lower major bleeding rates reported with recombinant TPA use may reflect more recent anticoagulation dosing regimens, low-dose weight-adjusted heparin, smaller sheath size, and imaging-guided venous access.

The initial anticoagulation dosage before catheter-directed thrombolysis is not different than the dosage for initial anticoagulation alone discussed above; however, vascular access should be obtained prior to anticoagulation to minimize access complications. Anticoagulation after catheter-directed thrombolysis should follow the recommendations stated in the initial anticoagulation section of this paper after the vascular access site sheath is removed. The recombinant TPA dosage suggested by the AHA for catheter-directed thrombolysis is 0.01 mg/kg/hr, and the suggested urokinase dosage is 120,000 to 180,000 units/hr. \(^{1}\) Periprocedural anticoagulation regimens should follow low-dose weight-adjusted unfractionated heparin dosing based on indirect evidence from arterial thrombolysis trials that demonstrated reduced major bleeding complications. The use of direct thrombin inhibitors or low molecular weight heparin during catheter-directed thrombolysis is not supported in the literature. Inferior vena cava filters were not routinely used during catheter-directed thrombolysis, and no current guidelines support their prophylactic use. Although the 2 small prospective catheter-directed thrombolysis trials mentioned above reported thrombolysis for a mean of 54 hours without the routine use of inferior vena cava filters, the rates of symptomatic pulmonary embolism were 1.3% and 0%.

**Percutaneous Mechanical Thrombectomy**

Percutaneous mechanical thrombectomy utilizes one of the multiple commercially available mechanical devices to aspirate, fragment, macerate, or disrupt venous thrombus. \(^{14}\) This technique is frequently used in combination with catheter-directed thrombolysis to remove fresh thrombus and minimize symptomatic pulmonary embolism. \(^{43-45}\) Although these 2 techniques are frequently used in combination to treat lower extremity DVT, the AHA guidelines indicate that performing percutaneous mechanical thrombectomy alone is reasonable if the patient has contraindications to thrombolytic agents; this suggestion seems to be based on expert opinion. The rationale for combined usage of these 2 techniques is supported by randomized trials that demonstrate percutaneous mechanical thrombectomy and catheter-directed thrombolysis together compared to catheter-directed thrombolysis alone are associated with major reductions \( (40\%-50\%) \) in hospital resources, infusion times, total dose of thrombolytic drug, number of catheterizations, and fluoroscopy time even though they have comparable rates of thrombus removal. \(^{46-53}\) The thrombolytic drug exposure reduction with percutaneous mechanical thrombectomy may decrease major bleeding complications, but no studies have evaluated the long-term benefits in the IFDVT patient subset. Inferior vena cava filter placement preprocedure and removal postprocedure are also reasonable if using percutaneous mechanical thrombectomy alone in patients with contraindications to thrombolytic drugs. \(^{46,54}\) Periprocedural anticoagulation dosage should follow the recommendations in the initial anticoagulation section of this paper if anticoagulants are used during percutaneous mechanical thrombectomy alone in patients with contraindications to thrombolytic drug use. \(^{1}\)
PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY AND STENT PLACEMENT

Percutaneous transluminal angioplasty and stents are often necessary to treat IFDVT outflow obstruction after successful thrombus removal with catheter-directed thrombolysis and percutaneous mechanical thrombectomy. The adjunctive use of percutaneous transluminal angioplasty and stents has been shown to prevent the recurrence of thrombosis, reduce PTS, improve quality of life, and enable healing of venous ulcers by removing the underlying venous outflow obstruction.55,56 Figure 2 shows the initial effect of percutaneous transluminal angioplasty with an optimal result after stent deployment. Deploying stents across the inguinal ligament and into the common femoral vein is acceptable if necessary to completely relieve venous outflow disease. May-Thurner or Cockett syndrome is a well-described syndrome associated with left-sided IFDVT caused by left common iliac vein compression from the overlying right common iliac artery (Figure 3). Percutaneous treatment with stent placement to prevent vessel recoil from external compression after thrombus removal is the treatment of choice for this syndrome.14,38,42,57,58

The prospective, multicenter catheter-directed thrombolysis registry for acute symptomatic lower extremity DVT reported by Mewissen et al demonstrated increased 1-year venous patency in patients who received iliac vein stents compared to those who did not.38 In 2 small retrospective studies, stents were used to treat iliac vein obstructive lesions after thrombectomy for acute IFDVT. In one study, Hartung et al reported a primary patency rate of 79% with iliac vein stenting at 1 year.59 In the other study, Mickley et al reported a decreased incidence of recurrent venous thrombosis with iliac vein stenting plus anticoagulation compared to anticoagulation alone (13% vs 73%, P<0.01) in patients who underwent transfemoral venous thrombectomy.60

Treatment of chronic total occlusive disease in iliac veins has demonstrated benefit by decreasing PTS, healing venous ulcers, and improving quality of life.55,56,61 Raju and Neglén reported a retrospective review of 159 patients with postthrombotic chronic total iliac vein occlusion who underwent attempted percutaneous revascularization.51 The acute procedural success rate was 83% (139 of 167 limbs) with a secondary stent patency rate of 66% at 4 years, relief of pain at 79% at 3 years, relief of swelling at 66% at 3 years, and cumulative healing of venous ulcers at 56% at 33 months. A significant improvement in quality of life metrics was also reported. Neglén et al published a large retrospective review (n=493) reporting 54-month stent patency in chronic total occlusions of the iliofemoral veins in patients with PTS. Stent patency was greater with cephalad compared to caudal stent termination in relation to the inguinal ligament (95% and 86%, respectively, P=0.0001). None of the braided stainless steel stents traversing the inguinal ligament was reported to be compressed or fractured in this review. Femoral vein stents—as opposed to femoral artery stents—can be safely placed across the inguinal crease with minimal effect on long-term patency.56 Hartung et al reported acute and long-term results of stenting for chronic iliocaval obstructive lesions (n=89).55 The acute
technical success rate was 98% with a primary patency rate of 83% at 3 years. Venous disability scores were also improved after revascularization. Periprocedural anticoagulation dosage should follow the recommendations in the initial anticoagulation section of this paper.

CONCLUSION

Patients with IFDVT represent an opportune subset of patients for acute interventional management with currently available techniques. This subset of patients with proximal DVT has a worse prognosis, is less well studied, and benefits more from acute intervention compared to all patients with proximal DVT or calf vein DVT. The increased morbidity and worse prognosis in this cohort of patients are partially because of the anatomy of lower extremity venous outflow. Invasive catheter-based therapies that remove thrombus and correct venous outflow obstructions improve outcomes and morbidity in patients with IFDVT. Future trials that address IFDVT specifically will improve our understanding and proper management of this higher-risk subset of DVT patients.

REFERENCES


