Treatment of Acute Iliofemoral Deep Venous Thrombosis: A Strategy of Thrombus Removal

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Patients with acute iliofemoral deep vein thrombosis (DVT) suffer the most severe postthrombotic sequelae. The majority of physicians treat all patients with acute DVT with anticoagulation alone, despite evidence that postthrombotic chronic venous insufficiency, leg ulceration, and venous claudication are common in patients treated only with anticoagulation. The body of evidence to date in patients with iliofemoral DVT suggests that a strategy of thrombus removal offers these patients the best long-term outcome. Unfortunately, currently published guidelines use outdated experiences to recommend against the use of techniques designed to remove thrombus, ignoring recent clinical studies showing significant benefit in patients who have thrombus eliminated. Contemporary venous thrombectomy, intrathrombus catheter-directed thrombolysis, and pharmacomechanical thrombolysis are all options that can be offered to successfully remove venous thrombus with increasing safety. The authors review evidence supporting the rationale for thrombus removal and discuss the most effective approaches for treating patients with acute iliofemoral DVT.

Keywords: Deep venous thrombosis; Catheter-directed thrombolysis; Venous thrombectomy; Pharmacomechanical thrombolysis; Percutaneous mechanical thrombectomy.

Introduction

Anticoagulation alone is the treatment used by most physicians for patients with acute deep venous thrombosis (DVT). Unfortunately, the extent of thrombosis has little or no bearing on the management decisions made by physicians when treating acute DVT.

The American College of Chest Physicians (ACCP) 6th Consensus Conference on Antithrombotic Therapy further diminished enthusiasm by physicians to adopt any strategy of thrombus removal as a result of their statements regarding operative venous thrombectomy and thrombolytic therapy. Buller et al. stated that “in patients with DVT, we recommend against the use of venous thrombectomy (Grade 1C).” The committee goes on to say that “surgical thrombectomy is commonly complicated by a recurrence of thrombus formation.” Unfortunately, the authors reference an anecdotal experience in patients treated over 40 years ago. The follow-up of these patients was incomplete and biased. Only 50% of the patients originally treated underwent follow-up and only 25% had repeat phlebography. As most physicians know, patients who have the worst clinical outcomes, in these cases postthrombotic morbidity, represent the majority of patients who return for follow-up care. Patients who have minimal or no ongoing symptoms are less likely to seek additional long-term medical care. It is unclear how Buller et al. could have overlooked a randomized trial of venous thrombectomy vs. anticoagulation with long-term follow-up. This prospective study documented significant benefit in patients randomized to thrombus extraction.

The ACCP consensus conference section stated that “there is no evidence that supports the use of thrombolytic agents for the initial treatment of DVT.” They recommended against the routine use of catheter-directed thrombolysis (Grade 1C), and they went on to state that thrombolytic therapy be confined to patients requiring limb salvage (Grade 2C). Most physicians recognize that delivery of a thrombolytic agent into the thrombus is considerably more effective than
systemic administration. This observation follows the basic mechanism of thrombolysis, which occurs by way of activation of fibrin-bound plasminogen.\textsuperscript{7} A randomized trial\textsuperscript{8} and a vast clinical experience have demonstrated the improved effectiveness of catheter-directed intrathrombus delivery of plasminogen activators.\textsuperscript{9–11}

Despite evidence demonstrating that patients with iliofemoral venous thrombosis suffer more severe postthrombotic morbidity than patients with infragenital deep venous thrombosis,\textsuperscript{12–14} the majority of physicians treat all patients with acute DVT with anticoagulation alone. A treatment approach that includes a strategy of thrombus removal and optimal anticoagulation\textsuperscript{15} has not been adopted by most clinicians, even in patients with the most extensive form of venous thrombosis.

It appears that patients with iliofemoral DVT are a clinically relevant subset of patients with acute DVT who suffer severe postthrombotic morbidity.\textsuperscript{12–14} Following anticoagulation alone for management of iliofemoral DVT, postthrombotic chronic venous insufficiency, leg ulceration, and venous claudication are common.\textsuperscript{12–14} It is the thesis of this report that when one considers the body of evidence to date in patients with extensive DVT, a strategy of thrombus removal is the preferred management and offers patients the best long-term outcome.

### Rationale for Thrombus Removal

The pathophysiology of chronic venous insufficiency is ambulatory venous hypertension, defined as an elevated venous pressure during exercise.\textsuperscript{16} Ambulatory venous pressure in the lower leg and foot generally drops to less than 50% of the standing venous pressure in normal individuals. In patients with the postthrombotic syndrome, the ambulatory venous pressure drops very little, and in individuals with persistent venous occlusion, the ambulatory venous pressure may actually rise above standing pressure. This degree of ambulatory venous hypertension often leads to the debilitating symptoms of venous claudication.

The anatomic components contributing to ambulatory venous hypertension are venous valvular incompetence and luminal obstruction. Studies consistently demonstrate that the most severe postthrombotic morbidity is associated with the highest venous pressures, which occur in patients with valvular incompetence accompanied by luminal venous obstruction.\textsuperscript{16,17} Venous obstruction is not synonymous with occlusion. Occlusion is complete obliteration of the lumen, whereas obstruction (in most patients) is relative narrowing of the lumen (Fig. 1). Unfortunately, technology has not advanced to the point that allows physicians to assess the pathophysiologic impact of partial luminal obstruction in an individual patient.

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Fig. 1. (A) Ascending phlebogram in a patient who had iliofemoral DVT 10 years earlier showed chronic venous disease with “no evidence of obstruction,” as stated on the x-ray report. Three-second maximal venous outflow performed with impedance plethysmography. A classic Linton procedure, which includes ligation of the femoral vein distal to its junction with the profunda, was performed. A cross-section of the femoral vein (B) illustrates recanalisation of the femoral vein with multiple channels showing significant luminal obstruction.
Therefore, physicians often cannot put venous obstruction into proper pathophysiologic perspective in terms of its contribution to postthrombotic morbidity. Therefore, there is widespread underappreciation regarding the importance of luminal obstruction contributing to postthrombotic morbidity.

Experimental observations in canine models of acute DVT demonstrated that thrombolysis preserves endothelial function and valve competence immediately and at four weeks after therapy compared with placebo. There was less residual thrombus in veins treated with a plasminogen activator, thereby preserving the vein’s structural integrity.18,19

These experimental observations translate into improved clinical outcomes as observed in a natural history study of acute DVT in patients treated with anticoagulation.20–22 These investigators found that patients with persistent proximal vein obstruction developed distal valvular incompetence, even when distal veins were not involved with thrombus.20 They confirmed that the combination of venous obstruction and valve incompetence was associated with the most severe postthrombotic morbidity.21 Spontaneous clot lysis naturally restored venous patency. Interestingly, if spontaneous lysis occurred early (within 90 days), valve function was frequently preserved.22 It is intuitive that successful elimination of thrombus (spontaneous, mechanical, or pharmacologically accelerated) will eliminate luminal obstruction and increase the likelihood of preservation of valve function. It follows that, in patients whose thrombus is resolved (or eliminated), postthrombotic morbidity will be avoided or significantly reduced.

**Outcomes of a Strategy of Thrombus Removal**

**Contemporary venous thrombectomy**

Advances in all methods of elimination of thrombus from the deep venous system have occurred during the past 10–15 years. Contemporary venous thrombectomy has substantially improved the early and long-term results of patients with extensive DVT compared to the initial reports.4–6,23–32 Major technical advances between the initial and contemporary procedures are listed in Table 1. The technical details of contemporary venous thrombectomy have been recently reported.30,33

An important randomized trial was reported by the Scandinavian investigators, comparing operative venous thrombectomy and arteriovenous fistula versus anticoagulation alone in patients with iliofemoral venous thrombosis. Peer-reviewed reports occurred at 6 months,4 5 years,5 and 10 years6 of follow-up. Patients randomized to venous thrombectomy demonstrated improved patency (P < 0.05), lower venous pressures (P < 0.05), less edema (P < 0.05), and fewer postthrombotic symptoms (P < 0.05) compared to anticoagulation. Interestingly, more patients undergoing venous thrombectomy preserved normal venous valve function in their femoropopliteal segment than patients treated with anticoagulation alone. Hence, elimination of iliofemoral thrombus (and proximal venous obstruction) protected the distal valves from the hemodynamic consequences of obstructed proximal veins and resultant valvular incompetence of the distal veins.20

**Catheter-directed thrombolysis**

The mechanism by which thrombolysis results in clot dissolution is the activation of fibrin-bound plasminogen to form the active enzyme plasmin, which dissolves clot.7 During thrombosis, GLU-plasminogen (circulating) is converted to LYS-plasminogen (in thrombus) as a result of binding to fibrin. LYS-plasminogen has more binding sites for plasminogen activators and is more efficiently activated to plasmin than GLU-plasminogen. Intrafemoral delivery naturally protects plasminogen activators from neutralization by circulating plasminogen activator inhibitor (PAI-1) and also protects the resultant active enzyme plasmin from instantaneous neutralization by circulating antiplasmins. Catheter-directed delivery of plasminogen activators into the thrombus accelerates thrombolysis, increasing the likelihood of a successful outcome. Accelerated lysis reduces the overall dose and duration of plasminogen activator infusion; therefore, it is reasonable to expect that complications also will be reduced.

Numerous reports have emerged demonstrating favorable outcomes of catheter-directed thrombolysis for acute DVT.9–11,34–38 Three large reports document approximately an 80% success rate9–11 (Table 2).
Initial success rates likely would have been higher if treatment had been restricted only to patients with acute iliofemoral DVT. However, as clinicians gained confidence with the technique, patients with more chronic thrombus were treated, resulting in lower overall success rates. In these 3 studies, 422 patients were treated with consistent rates of success and complications. Importantly, underlying iliac vein stenoses were treated with balloon angioplasty, stenting, or both to achieve unobstructed venous drainage into the vena cava, thereby reducing the risk of recurrent thrombosis.

Major bleeding complications occurred in 5–10% of cases, with the majority occurring at the puncture site. Fortunately, intracranial bleeding was rare, occurring in only 3 patients in the National Venous Registry. Symptomatic pulmonary embolism (PE) occurred in 1% of patients in the series reported by Bjarnason et al. and the National Venous Registry and fatal PE occurred in only one out of the 422 patients. Therefore, death as a result of catheter-directed thrombolysis was rare.

An interesting therapeutic approach was reported by Chang et al. when they used intrathrombus bolus dosing of rt-PA in 12 lower extremities of 10 patients with acute DVT. They infused rt-PA intrathrombus using the pulse-spray technique, limiting a single treatment session to 50 mg. Following the pulse-spray bolus, patients were returned to their rooms and brought back the following day for repeat phlebographic evaluation and repeat infusion if necessary. Treatment was repeated up to four times. Eleven of the 12 extremities had significant or complete lysis, and one had 50–75% lysis. Although the average total dose of rt-PA was 106 mg, bleeding complications were minor and no patient dropped their haematocrit more than 2%. This intriguing technique deserves further study to evaluate its applicability to the general population of DVT patients.

The National Venous Registry reported 287 patients treated in both academic and community medical centres. Sixty-six percent had acute DVT, 16% had chronic, and 19% had an acute episode superimposed upon a chronic condition. Seventy-one percent of the patients presented with iliofemoral DVT and 25% with femoropopliteal DVT. Catheter-directed thrombolysis with intrathrombus infusion of urokinase (UK) was the preferred approach. In the subgroup of patients with acute, first-time iliofemoral DVT, 65% of the patients enjoyed complete clot resolution.

During follow-up, thrombus-free survival was observed in 65% at 6 months and in 60% at 12 months. There was a significant correlation ($P < .001$) of thrombus-free survival with the results of initial therapy. Seventy-eight percent of patients with complete clot resolution initially had patent veins at 1 year, compared to only 37% of those in whom <50% of the clot was dissolved. Interestingly, in the subgroup of patients with acute, first-time iliofemoral DVT who had initially successful thrombolysis, 96% of the veins remained patent at 1 year. In addition to sustained patency, early success directly correlated with valve function at 6 months. Sixty-two percent of patients with <50% thrombolysis had venous valvular incompetence, whereas 72% of patients who had complete lysis had normal valve function ($P < .02$).

Patients with iliofemoral DVT treated in the National Venous Registry were compared to a contemporary cohort of patients with iliofemoral DVT treated with anticoagulation alone in the same institutions. Anticoagulated patients were candidates for lytic therapy but were treated with anticoagulation alone due to physician preference. A validated quality-of-life (QOL) questionnaire was used to query patients at 16 and 22 months post treatment. Of the 98 patients evaluated, 68 were treated with catheter-directed thrombolysis and 30 treated with anticoagulation alone. Those treated with catheter-directed thrombolysis reported significantly better QOL than those treated with anticoagulation alone. Quality-of-life results were directly related to the initial success of thrombolysis. Patients who had a successful lytic outcome reported a significantly better health utilities
index, better physical functioning, less stigma of chronic venous disease, less health distress, and fewer overall postthrombotic symptoms. Patients in whom catheter-directed thrombolysis failed had similar outcomes to patients treated with anticoagulation alone. These efficacy data combined with the observed reduction in complications with intrathrombus infusion of plasminogen activators offer a solid argument for the management of patients with iliofemoral DVT with catheter-directed thrombolysis.

Subsequently, a randomized trial was performed by Elshawary et al.\textsuperscript{40} comparing catheter-directed thrombolysis to anticoagulation alone. These authors demonstrated that catheter-directed thrombolysis offered significantly better outcomes at 6 months. Assuming patients are properly managed with anticoagulation, this six-month observation should reflect their long-term outcome.

**Pharmacomechanical Thrombolysis**

No fewer than 10 percutaneous mechanical thrombectomy techniques have been developed. There appears to be a higher incidence of embolic complications with mechanical thrombectomy. Pulse-spray pharmacomechanical thrombolysis of clotted hemodialysis grafts has demonstrated an 18\% incidence of PE in patients treated with a plasminogen activator pulse-spray solution compared to a 64\% incidence of PE in patients treated with a heparinised saline pulse-spray solution ($P = .04$).\textsuperscript{41} Since the haemodialysis graft is in direct communication with the venous circulation, it appears that results in these patients should be similar to patients with proximal acute DVT. However, one would expect observations to be magnified when treating thromboses in the much larger veins.

In an experimental model comparing mechanical, pharmacomechanical, and pharmacologic thrombolysis, Greenberg and associates\textsuperscript{42} reported findings consistent with Kinney et al.\textsuperscript{41} Greenberg et al.\textsuperscript{42} demonstrated that pulse-spray mechanical thrombectomy was associated with the largest number and greatest size of distal emboli. Embolic particles diminished in number and size and the speed of lysis increased when a plasminogen activator (UK) was added to the pulse-spray solution. Catheter-directed thrombolysis alone was associated with the slowest rate of reperfusion but also the fewest number of distal emboli. Generally speaking, pharmacomechanical thrombectomy alone most often is inadequate. Hemolytic complications of rheolytic mechanical thrombectomy are common and occasionally can result in anemia and renal dysfunction.

Several percutaneous mechanical thrombectomy devices have recently been used either alone or in conjunction with thrombolytic therapy for acute iliofemoral DVT. A number of devices deserve further mention. The Amplatz device utilizes a rotational blender-like impeller design rotating at 100,000 rpm to aspirate and re-circulate macerated thrombus. Removal of thrombus is reported at 75–83\% in lower extremity acute DVT with 6 month patency of 77\%.\textsuperscript{43,44} Although transient procedural-related desaturation resolved shortly after catheter deactivation, there were no occurrences of clinically significant PE.\textsuperscript{44}

Rotational design was also adopted by the Arrow-Trerotola device, consisting of 4 helically arranged nitinol wires driven by a handheld battery-powered engine rotating the catheter head at 3000 rpm. Thrombus is macerated and re-circulated. In vitro studies have shown 99\% thrombus removal by weight with no remaining thrombus within the synthetic silicon grafts.\textsuperscript{45} When used clinically in addition to thrombolytic therapy and angioplasty with stents, technical and clinical success was reported in 100\% of patients with a 16-month clinical success of 92\%.\textsuperscript{46} Concerns with valve and intimal damage, although justified, have not been reported.\textsuperscript{46}

The AngioJet device has an entirely different design, using a high-velocity saline jet (350–450 km/hr) to produce a zone of negative pressure (–760 mmHg) around the catheter tip. Theoretical advantages of this design include less vessel trauma and the ability to aspirate thrombus particles through the exhaust port. In a study without adjunctive preprocedural thrombolytic therapy, Kasirajan et al.\textsuperscript{47} reported that half of the patients treated had ≥50\% of their thrombus removed. Patency was restored in 77\% of those patients with ≥50\% thrombus removal. Improved results have been observed in a similar study in which the AngioJet was used without preprocedural thrombolytics.\textsuperscript{48} Sixty-five percent of patients had complete thrombus removal while partial thrombus removal was observed in the remaining 35\%.\textsuperscript{48}

A new device recently released for segmental and controlled pharmacomechanical thrombolysis is the re-engineered Trellis\textsuperscript{®} catheter (Bacchus Vascular, Santa Clara, CA). This is a hybrid catheter which isolates the thrombosed vein segment between two occluding balloons. The plasminogen activator is infused into the thrombus between the occluding balloons. A dispersion wire is inserted into the catheter, resulting in the catheter shaft assuming a spiral configuration that, when activated, spins at 1500 rpm. After 15–20 minutes, the liquefied and particulate thrombus is aspirated. Phlebographic evaluation of the result is
performed before treating additional segments of thrombosed vein. The advantages of such a device are its ability to incorporate mechanical and pharmacologic therapies, even in patients with a contraindication to thrombolytic therapy, since the infusate is aspirated, and the rapidity with which treatment can be achieved. The rationales behind the design of this catheter are 1) rapidly resolving thrombus during a short course of treatment, 2) limiting or avoiding systemic thrombolysis by reducing exposure to plasminogen activators as a result of aspirating liquefied thrombus and infused plasminogen activator, and 3) preventing PE by proximal balloon occlusion. A clinical trial designed to evaluate the success and complication rate of this technique is currently underway.

Fig. 2. (A, B) Ascending phlebogram of a patient presenting with phlegmasia cerulea dolens of his left leg. Phlebogram shows extensive venous thrombosis of the femoral vein inclusive of the iliac vein which extends to the junction with the vena cava. Not shown is thrombus in the posterior tibial and popliteal veins. The patient was treated with segmental pharmacomechanical thrombolysis. (C) The Trellis catheter (Bacchus Vascular, Santa Clara, CA) is in place with balloons inflated. Segmental pharmacomechanical thrombolysis successfully lysed clot (D) and restored patency to the iliofemoral venous system. The posterior tibial and popliteal thrombosis was treated with ultrasound-accelerated thrombolysis using the EKOS LysUS system (EKOS Corp, Bothell, WA). (E) The EKOS catheter was inserted into the posterior tibial vein at the ankle and advanced into the popliteal vein. (F–H) Completion ascending phlebography demonstrates complete clot lysis from the posterior tibial vein to the vena cava. The patient’s leg normalized and he became asymptomatic.
The emission of ultrasound waves from an infusion catheter delivering the plasminogen activator is an interesting new adjunct to catheter-directed thrombolysis. Reports have emerged indicating that an infusion catheter with ultrasound transducers built into the infusion end of the catheter accelerates thrombolysis. Ultrasound enhancement of the fibrinolytic activity of tissue plasminogen activator has been observed in vitro. This effect is the result of clot fibrin fragmentation, increasing exposed fibrin surface and thereby allowing greater tPA binding to fibrin due to its larger available surface area. In vivo models and clinical trials are now underway to assess the potential value of ultrasound enhancement of thrombolysis for the management of acute DVT.

A patient presenting with phlegmasia cerulea dolens two days after laparotomy (Fig. 2) illustrates the advantage of using segmental pharmacomechanical thrombolysis and ultrasound-accelerated catheter-directed thrombolysis in order to shorten treatment duration and limit exposure of the thrombolytic agent, yet maximizing the chance of a successful result.

Thrombolysis is effective in restoring venous patency and has become safer with the direct intrathrombus infusion and adjunctive mechanical techniques. As technology continues to improve and as direct clot-dissolving pharmacologic agents are developed, lytic infusion times should considerably shorten and complication rates will be significantly reduced.

Recommendations for Management of Patients with Iliofemoral DVT

The general treatment strategy for patients with acute iliofemoral DVT is summarized in the algorithm illustrated in Fig. 3. Few patients need to be treated as an emergency; however, all patients are immediately anticoagulated, placed in snug, long-leg, multilayered compression bandages extending from the base of the toes to the upper thigh, and treated with leg elevation. Patients are encouraged to ambulate following anticoagulation. When not ambulating, patients are in bed with their legs elevated.

A rapid computed tomography (CT) scan with contrast is performed of the chest, abdomen, and pelvis to evaluate for PE and other pathology, which may be associated with their aggressive degree of thrombosis (Fig. 4). Patients who are physically active are considered for a strategy of thrombus removal. Generally, for patients who are minimally active or have an expected lifespan of less than 2 years, anticoagulation with compression is recommended. Patients who have a free-floating thrombus in their vena cava usually have a vena caval filter inserted prior to catheter-directed thrombolysis.

Patients considered for a strategy of thrombus removal who have a contraindication to thrombolysis are treated either with a contemporary venous thrombectomy or segmental pharmacomechanical thrombolysis using the Trellis catheter. Patients who have no
A contraindication to thrombolysis are offered catheter-directed thrombolysis, usually with the addition of pharmacomechanical techniques. Once the thrombus is removed, patients are evaluated for an underlying venous lesion, which should be corrected to provide unobstructed venous drainage into the vena cava, thereby reducing the risk of recurrent thrombosis. Subsequently, early and long-term therapeutic anticoagulation is important to avoid recurrent thrombosis. Intermittent pneumatic compression units are applied while patients are in bed during their hospitalization.

Therapeutic long-term anticoagulation is important to avoid recurrent thrombosis. Since these patients have demonstrated an aggressive propensity for thrombosis compared to the majority of DVT patients, we tend to treat these patients with a longer duration of anticoagulation, at least one year with most patients treated much longer. These patients generally have a low risk of bleeding complications but face serious morbidity if rethrombosis occurs. When we consider terminating anticoagulation, we obtain a venous duplex examination to evaluate for residual venous thrombus, and we check for evidence of thrombus activity by attaining D-dimer levels. If the venous duplex shows persistent venous thrombus and/or the D-dimer level is elevated, anticoagulation is continued.

If an underlying aetiology for the patient’s extensive venous thrombosis cannot be identified, a thrombophilia evaluation is performed. The majority of these patients do not have an identifiable cause (e.g., metastatic or extensive cancer) for their aggressive thrombosis; therefore, the majority undergo a thrombophilia evaluation.

Discussion

Postthrombotic morbidity following iliofemoral DVT is certain. The more extensive the thrombosis
and the more active the patient, the more severe the postthrombotic sequelae. Patients who are active and those with an anticipated survival of 2 or more years should be offered a strategy of thrombus removal.

Long-term benefits of a strategy of restoring venous patency have been documented in a randomized trial of venous thrombectomy. Likewise, randomized trials of systemic thrombolysis therapy show that when it is successful, patients have fewer postthrombotic sequelae and improved venous function compared to patients treated with anticoagulation alone or when lytic therapy is unsuccessful. A national randomized trial is being planned, which should definitively answer the question as to whether methods to achieve thrombus removal will be successful, and can be applied safely.

Improvements in operative technique as well as catheter-based technology now document higher rates of success and complication rates which are acceptable. As clinicians become more experienced with these techniques, technology continues to improve, and new pharmacologic agents are developed that lyse thrombus more rapidly with fewer bleeding complications, the application of these principles should expand.

A national randomized trial is being planned, which should definitively answer the question as to whether a strategy of thrombus removal is more effective than anticoagulation alone in reducing postthrombotic sequelae. Until that trial is completed, the available information strongly supports offering a strategy of thrombus removal for patients with acute, symptomatic iliofemoral DVT.

References


