Endovascular Intervention of Iliofemoral Venous Thrombosis

Is there a role for percutaneous pharmacomechanical thrombectomy?

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It is estimated that deep vein thrombosis (DVT) affects approximately 50 per 100,000 people annually in the US based on large epidemiological studies, with an in-hospital case-fatality rate from complications of thromboembolism at 12%. It has also been shown that 300,000 hospitalizations per year in the US can be directly attributed to venous thrombotic disease, with studies reporting as many as 90% of patients traditionally admitted to the hospital. It is also estimated that DVT affects 20% to 30% of all major surgical patients and, as a result of pulmonary embolism, is responsible for more than 60,000 deaths annually in the US. Venous thromboembolic disease, both DVT and pulmonary embolism (PE), is an underdiagnosed medical problem that frequently results in high rates of severe morbidity and mortality. Most studies cite inadequate venous thrombotic prophylaxis in surgical and medical patients as a causative factor in DVT and PE. Regardless of the occurrence of PE, DVT alone can negatively impact patient outcomes and increase health care costs. Patients with multiple venous segment involvement, particularly in the iliofemoral veins, are among those most frequently hospitalized for treatment.

Endovascular interventions of acute DVT using various therapeutic modalities, such as thrombolysis, mechanical thrombectomy, and inferior vena cava (IVC) filter placement have received increased focus among health care providers in the past decade, a phenomenon that is possibly fueled by several factors. A significant advance has taken place in the current medical management of DVT, as the pharmaceutical industry has developed many effective and convenient outpatient medications using low-molecular-weight heparin in the treatment of acute DVT. This has generally resulted in improved patient compliance and reduced hospitalization compared to the conventional intravenous heparin anticoagulation. The improvement in medical therapy has also heightened the awareness of primary care physicians and the general public regarding the clinical sequelae of DVT. As a result, patients with symptomatic venous thromboembolism are...
DVT. This condition consists of a wide spectrum of clinical
manifestations. Symptoms can be minor (ie, telangiectases
or varicose veins) or more troublesome (ie, swelling and
pain). Skin changes with lipodermatosclerosis and ulcera-
tions are some of the most severe manifestations. The in-
cidence of postthrombotic syndrome after proximal venous
thrombosis has been measured at 16% to 82%.7,11-14 The
incidence of ulceration has been estimated at 3% to 8%
after DVT.7,12,15,16

There is some controversy about the pathophysiology of
postthrombotic syndrome. Some investigators have indicat-
ed that the primary mechanism is reflux,14,17 whereas others
have found that it is the combination of reflux and obstruc-
tion that leads to the most severe symptoms.18,19 Johnson et
al reported on a natural history study of DVT.20 Legs were
evaluated with duplex ultrasound 1 to 6 years after an acute
DVT demonstrated that there was a significant difference
between the legs that developed postthrombotic syndrome
compared to those that remained normal. The study
showed that the finding of a combination of reflux and
obstruction was 3.5 times more likely in legs with evidence
of postthrombotic syndrome than in legs that appeared
normal. Interestingly, there were several patients who had
combined reflux and obstruction and no signs of venous
insufficiency. The investigators proposed that they would
have to follow the patients with abnormal duplex findings
but without clinical manifestations to see what their out-
come would be over time. In support of this comment is a
population-based study by Mohr et al21 who reported the
natural history of patients with a history of DVT. Mohr et
al found that there was a progressive increase of postthrom-
botic syndrome over 20 years. Patients at highest risk were
those younger than 40 years with proximal DVT. This group
was also three times more likely than other groups to devel-
oping postthrombotic symptoms.

The relationship of the duration of venous occlusion and
the likelihood of secondary reflux clearly has been demon-
strated.22 Meissner et al showed with serial duplex ultra-
sonography that veins that achieved competence after
venous thrombosis became recanalized 2.3 to 7.3 times faster
than veins that became incompetent. This was shown to be
most important for the proximal veins.22 Similarly,
O’Shaughnessy and Fitzgerald found that earlier lysis led to
preserved valvular function and fewer symptoms.14 Markel
et al demonstrated a progressive deterioration of valvular
competence in legs with DVT that continues to worsen dur-
ing the first 12 months.23 The extent of the original DVT has
been associated with an increased incidence of postthrom-
botic syndrome. Multilevel disease and recurrent thrombo-
sis are the two factors reported by Ziegler as being highly
predictive of the development of chronic venous insufficien-
cy.24 Widmer describes more sequelae of postthrombotic
syndrome with multilevel thrombosis.25 In particular,

CLINICAL CONSEQUENCES OF DVT

Postthrombotic syndrome, a clinical entity of chronic
venous insufficiency, represents a long-term sequelae of
DVT. This condition consists of a wide spectrum of clinical
consequences of DVT

Acute iliofemoral DVT, which was treated with rheolytic
thrombectomy, is discussed. Last, an illustrative case of
thrombolysis (complete and partial lytic success) versus
those treated with anticoagulation alone derived significant
benefit in terms of improvement of quality of life.

Endovascular management utilizing percutaneous
mechanical thrombectomy alone or in combination with
pharmacological thrombolytic agents has recently received
much attention in the literature as a safe and effective
means for the treatment of acute DVT.4,10 Along with possi-
ble preservation of venous valve function, this treatment
strategy also permits simultaneous correction of inciting
anatomic lesions, such as iliac vein stenosis. In this article,
the clinical data on various endovascular treatment modal-
ities, with a particular focus on pharmacomechanical
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acute iliofemoral DVT, which was treated with rheolytic
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The indications of venous thrombolysis in acute DVT, as
well as the ideal thrombolytic agent of choice, have been a
subject of debate. Although anticoagulation is effective in
preventing PE, many patients go on to experience the con-
sequences of postthrombotic syndrome, which is a chronic
sequela of DVT, with resultant valvular insufficiency of the
lower extremity. It is well documented that lytic therapy
leads to a more rapid and complete dissolution of clot com-
pared with heparin treatment alone.5-8 Complete clot disso-
lution was observed in 35% of patients undergoing lysis ver-
sus 4% of those treated with heparin alone. The concept of
early venous thrombolysis has been promoted by the
iliofemoral venous thrombosis registry,9 which is a multicen-
ter registry designed to determine the role of catheter-
directed thrombolysis in the treatment of DVT as com-
pared to systemic heparin anticoagulation. The study found
no differences in mortality rates or in the incidence of PE
between the two groups, although bleeding complications
were seen in 17% of the lytic group and 4% of the heparin-
treated group. Patients having successful catheter-directed
thrombolysis (complete and partial lytic success) versus
those treated with anticoagulation alone derived significant
benefit in terms of improvement of quality of life.

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patients with iliofemoral DVTs have been noted to do poorly in terms of physiologic function of the veins.\textsuperscript{26}

**TREATMENT STRATEGIES**

Various treatment modalities have been utilized successfully in the management of iliofemoral venous thrombosis. As our current understanding regarding the pathophysiology of venous thromboembolism continues to expand, coupled with constant refinements of endovascular devices in thrombotic therapy, the ideal treatment strategies for venous thrombosis will continue to evolve.

**Anticoagulation**

Conventional treatment of DVTs, including iliofemoral DVTs, continues to be anticoagulation. Bates and Ginsberg recommend full anticoagulation for a duration of 3 months to a lifetime.\textsuperscript{15} The duration depends on the risk of recurrence as determined by the presence or absence of an inciting event and the presence of hypercoagulable states. Anticoagulation, however, only prevents clot propagation and relies on the patient’s own fibrinolytic system to open occluded segments to restore patency and preserve valvular function.

**Surgical Thrombectomy**

Enthusiasm for surgical thrombectomy for DVT in the US was initially high, but has fallen with reports of poor results.\textsuperscript{27} Serial reports of the European results have rekindled interest, however. In a series of reports, Plate et al have described surgical therapy for acute iliofemoral DVT.\textsuperscript{28,29} These reports detail the experience of patients randomized to anticoagulation versus surgical thrombectomy with creation of a temporary arteriovenous fistula followed for 5 and 10 years. The numbers of those completing follow-up are small, reducing the ability to produce statistical significance. Radio-nucleotide venous study showed patency of the iliac vein in 83% of patients with surgical treatment compared to 41% of patients with anticoagulation, which was significant. Venous physiology and postthrombotic symptoms were both worse in the group with anticoagulation.

**Thrombolytic Therapy**

In light of the morbidity of postthrombotic syndrome, more aggressive treatment regimens of DVTs have been proposed. The early reports of surgical thrombectomy and its impact on postthrombotic syndrome encouraged development of nonsurgical methods to remove clot and achieve the same goals by minimally invasive means. Thrombolysis of DVTs offers the potential to rapidly clear thrombus from the obstructed segments and reduce the chance of subsequent obstruction and reflux; a review by Comerota and Aldridge of 13 studies comparing thrombolysis versus anticoagulation confirmed this hypothesis.\textsuperscript{5} In this study, complete or significant lysis was achieved in 4% of patients with anticoagulation and in 45% of patients with thrombolysis. Successful lysis in long-term follow-up was associated with a lower incidence of postthrombosis syndrome and improved venous function.

Several thrombolytic agents are available for thrombolytic therapy. The basic mechanism of these agents is to activate plasminogen, which then acts to break down fibrin. Streptokinase was the first agent used for thrombolysis. Later, urokinase (Abbokinase, Abbott Laboratories, Abbott Park, IL) and the plasminogen activators became available. There are claims of varying degrees of efficacy and potential for complications. Schweizer et al found that urokinase was more effective,\textsuperscript{30} whereas Sugimoto et al found that rt-PA (Alteplase, Activase, Genentech, San Francisco, CA) worked more quickly.\textsuperscript{31} A retrospective review has also been done to compare the various fibrinolytic agents in the treatment of DVTs. Grunwald and Hofmann reported that urokinase and the plasminogen activators were essentially equal in terms of efficacy and complication rates.\textsuperscript{32} The only significant difference was the increased cost associated with urokinase. This same finding has been observed in a comparison in a mixed population of patients with arterial and venous disease treated with thrombolysis.\textsuperscript{31}

**Systemic Thrombolytic Therapy.** The first descriptions of thrombolysis for DVTs were systemic infusions or regional infusions. Regional or “locoregional” infusions are delivered through a vein in the foot with a firm bandage on the extremity to direct the thrombolytic agent into the deep venous system.\textsuperscript{33} Comparison of regional and systemic infusions has shown the two methods to be essentially equal in efficacy.\textsuperscript{30,34} This is intuitive because the agent is likely to travel through remaining open veins rather than bathing the clot in occluded segments.

Early reports documented success in treating phlegmasia with streptokinase, with enthusiastic reports of excellent results that were beyond expectation.\textsuperscript{35} Martin and colleagues found a 60% rate of total or partial lysis with urokinase.\textsuperscript{34} Goldhaber and associates reported a series of patients treated with systemic urokinase and had a 52% response to thrombolysis as measured by a combination of ultrasound and venographic follow-up.\textsuperscript{36} An early randomized trial by Common et al compared streptokinase with heparin at 7-month follow-up with clinical evaluation and venography.\textsuperscript{37} They discovered 40% normal veins in the thrombolysis group compared with 8% in the heparin group. The majority of the heparin group had recanalization, but with a significantly higher incidence of valvular reflux. Watz et al reported another randomized trial of streptokinase versus heparin.\textsuperscript{38} Complete lysis and preservation of valvular function was noted in 44% and 92% of
patients, respectively, with thrombolysis compared with 6% and 13% of patients with heparin. A randomized trial by Turpie et al with rt-TPA demonstrated a thrombolytic efficacy greater than 50% occurred in 58% of patients, which was in sharp contrast to none of the patients in the heparin group. Patients with successful lysis had a 25% incidence of postthrombotic symptoms compared with 56% of patients without successful lysis.

Not surprisingly, thrombolysis of acute DVT is more effective than chronic venous thrombus. D’Angelo and associates found that lysis worked better on clots younger than 8 days and best on those of younger than 5 days, with a success rate in that group of 61%. This experience of better outcomes with treatment of acute DVTs has been mirrored by others.

Not all reports of systemic thrombolysis had favorable results. In a report of 250 patients with systemic or local therapy with rt-PA, streptokinase, or urokinase, Schweizer et al found significantly greater patency and reduced incidence of postthrombotic syndrome in the group with lysis. When taking into account a 5% major bleeding complication rate and an apparent increase in PE, however, they recommended selective use for limb-threatening situations only. No benefit to systemic thrombolysis was found by Schwieder et al, who determined a lysis rate of only 33%, which was nearly equal to the complication rate. Similarly, Kil and colleagues found no benefit to systemic thrombolysis in a trial comparing urokinase and heparin. Most patients improved clinically, but the venographic findings were not statistically different between the two groups. Lastly, Goldhaber et al demonstrated a disappointing 29% rate of significant lysis with systemic rt-PA and had one intracranial hemorrhage.

Although some investigators have reported no bleeding complications with systemic thrombolysis, others have reported bleeding complication rates from 18% to 33%. Most of these reported complications are of bleeding at the puncture site and are reported as major if they required transfusion. These reports are magnified, however, by the report of an 8% mortality rate in the series of patients treated with systemic streptokinase. A review of six studies of systemic thrombolysis demonstrated that thrombolysis was achieved 3.7 times more often than anticoagulation, but with the consequence of 2.9 times the incidence of major bleeding complications. A subsequent review of 13 studies, including both systemic and catheter-directed thrombolysis, demonstrated that iliofemoral thromboses were more likely to fail with systemic treatment.

Catheter-Directed Thrombolytic Therapy: Attention has turned to catheter-directed thrombolysis because of the inconsistent results, long treatment times, and high complication rates reported with systemic infusions.

Intrathrombus infusion in DVTs is logical, given experience in the arterial system. An animal model study compared thrombectomy and catheter-directed thrombolysis and found less residual thrombus, better endothelial function, and a trend toward better valvular competence in the lysis group.

One of the earlier studies of catheter-directed thrombolysis for DVTs was reported by Okrent et al in 1991. Semba and Dake reported a series of 21 patients with iliofemoral DVTs treated with catheter-directed urokinase infusions. Lysis was complete in 72% and partial in 20% of patients, two chronic occlusions could not be treated, and there were no major complications in this series. Another series of 77 patients who underwent catheter-directed urokinase infusions for DVTs was reported by Bjarnason et al, who found secondary patency rates of 78% for iliac veins and 51% for femoral veins. Patients with symptoms for longer than 4 weeks or who had a malignancy did worse. No intracranial hemorrhage occurred, and only two patients had bleeding that required transfusion. A series of 24 patients with acute iliofemoral DVTs treated with catheter-directed rt-PA infusions was reported by Verhaeghe et al in 1997, who had a 79% successful restoration of patency rate and a puncture site bleeding complication rate of 25%.

The report of Semba led to the creation of the venous registry. Mewissen et al published the results of this multicenter experience of catheter-directed urokinase infusion in 1999. Two hundred eighty-seven patients were included in this series, and complete lysis was noted in 31% of patients, with another 52% having greater than 50% lysis. The degree of lysis was found to correlate with patency at 1 year. The DVTs in the iliofemoral segment responded better, with a 64% 1-year patency rate compared with 47% in the femoral popliteal segment. Major bleeding complications occurred in 11% of patients, with the majority being puncture site hematomas. There was one intracranial hemorrhage, which was fatal, and one subdural hematoma was sustained after a fall. There were PEs in 2% of patients, which was believed to be within the expected incidence for patients with proximal DVTs.

AbuRahma et al published a 10-year experience in patients with iliofemoral DVTs who were given the choice of anticoagulation versus catheter-directed thrombolysis. At 5-year follow-up, the group with lysis had a 69% venous patency rate and a 22% postthrombotic symptom rate compared to an 18% patency rate and a 70% symptomatic rate in the anticoagulation group. Elsharawy and Elzayat published the only randomized trial of catheter-directed thrombolysis versus anticoagulation in iliofemoral DVTs in 35 patients in 2002. At 6 months, the group treated with thrombolysis had 72% patency and 11% reflux rates compared with 12% patency and
42% reflux rates in the anticoagulation group. In a small series of 12 patients with iliofemoral DVTs treated with catheter-directed rt-PA infusions, Sillese et al found that 10 of 12 patients had a patent competent vein at 5-month follow-up.\(^5^5\)

Multiple investigators have found that catheter-directed therapy is more effective than systemic infusion of thrombolytics for treatment of DVTs.\(^5^6\) Although the numbers are small, and the trial was nonrandomized, the data reported by Laiho et al provide a comparison between systemic and catheter-directed thrombolysis for iliofemoral DVTs.\(^5^6\) Using a hospital registry, they identified 32 patients with iliofemoral DVTs. The patients were split equally between catheter-directed and systemic thrombolysis. Catheter-directed thrombolysis proved to be superior, with a deep system competence of 56% compared to 19% in patients with systemic thrombolysis. Paralleling the incidence of deep system reflux was a significantly higher incidence of postthrombotic syndrome in the systemic therapy group.

A large review of randomized trials comparing thrombolysis (both systemic and catheter-directed) was reported.\(^5^7\) Only 12 trials met inclusion criteria, and all but one were systemic infusions. The main findings were improved venous patency and decreased postthrombotic syndrome in thrombolysis patients. There was a trend toward decreased bleeding complications over time, with closer attention to risk factors for bleeding. A review by Baldwin et al documents the experience in the literature of more than 600 patients with catheter-directed thrombolysis and found decreased postthrombotic syndrome, improved quality of life, and some evidence for reduced incidence of recurrent DVT.\(^5^8\) The pooled risk of intracranial hemorrhage was noted to be 0.2%.\(^5^8\)

**Mechanical Thrombectomy**

Although a detailed discussion of percutaneous mechanical thrombectomy (PMT) in DVT is beyond the main focus of this discussion, this therapeutic modality has become an important tool in the armamentarium for managing thrombotic occlusion, particularly when a mechanical thrombectomy device can be used in conjunction with pharmacologic thrombolysis. It is noteworthy that presently no thrombectomy device has received FDA approval for DVT intervention. One of the PMT systems that has been shown to be effective in removing acute DVT is the Angiojet Rheolytic Thrombectomy System. The principal mechanism of action of this device is based on the Venturi effect, which creates rapidly flowing saline jets that are directed backward from the tip of the device to outflow channels in a coaxial fashion. This generates a vacuum force that draws the thrombus into the catheter (Figure 1).

One major advantage of this percutaneous treatment modality is that the thrombectomy catheter can be delivered through a small-bore introducer sheath, which reduces access site trauma and avoids operative arterial exposure required with the conventional Fogarty thromboembolec- tomy. A clinical study that evaluated the efficacy of the Angiojet system has demonstrated that such a mechanical thrombectomy system is effective in thrombus removal, venous patency restoration, maintenance, and symptom relief.\(^6^\) The Angiojet Rheolytic Thrombectomy System is designed to produce an area of extremely low pressure at the catheter tip by controlled high-velocity saline jets. Via this mechanism, thrombus surrounding the catheter tip is macerated and rapidly evacuated via an effluent lumen into a collection chamber. In this study, only four (23.5%) patients achieved >90% thrombus clearance with percutaneous mechanical thrombectomy alone. Adjunctive thrombolytic agents were used in nine of 17 patients, those that had a lesser amount of clot extracted with the use of the percutaneous mechanical thrombectomy catheter. Often, the thrombolytic catheter was left in place, and the average duration of lytic therapy was 20.2 hours. Clinical symptomatic improvement was seen in 82% over a follow-up time frame of 11 months.\(^6\)

**Pharmacomechanical Thrombectomy**

Combining percutaneous mechanical thrombectomy devices with thrombolytic agents, also known as pharmacomechanical thrombectomy, has great appeal because it can potentially reduce the overall dosage of the thrombolytic agents, as well as decrease the duration of thrombolytic therapy.\(^1^0\) The concept of pharmacomechanical therapy using the Angiojet Rheolytic Thrombectomy System was recently approved by the FDA for clinical application. The following technical descriptions are based on the authors’ preference when performing a pharmacomechanical thrombolytic therapy utilizing the Angiojet system. All procedures are performed in a fully equipped operating room with endovascular capabilities. The patients are placed in the prone position, and the ipsilateral popliteal vein is cannulated using ultrasound guidance and a micropuncture technique. After the initial ascending venogram is obtained, the Angiojet catheter is advanced over a guidewire and through the thrombosed vein segment. At this point, adjunctive thrombolytic agent is added to the infusion solution. One slow pass, withdrawing the catheter, is made to dissolve the thrombus with the thrombolytic agent and aspirate loose fragments. The catheter’s design is such that it allows for thrombus fragmentation and rapid evacuation through the effluent lumen. This sequence may be repeated if significant residual thrombus remains on subsequent venograms. If residual venous stenosis is found at the
completion of the thrombolytic therapy, additional intervention such as venous stenting may be performed, if clinically indicated.

**Adjuvant Therapy With Angioplasty and Stenting**

An important point to consider is that many patients have an anatomic abnormality that predisposes them to DVT and can be discovered and treated during thrombolytic therapy. Virchow originally described what would become known a century later as May-Thurner syndrome. Although there are many variants, the most common manifestation is compression of the left common iliac vein by the crossing right common iliac artery. Corroborating evidence for this is the finding that multiple investigators report extensive DVT more commonly on the left side than the right.

Stenting of this lesion has been shown to be durable, with >90% patency at 1 year. Investigators who report the need for adjuvant angioplasty and stenting describe the incidence to be between 34% and 64%. In one report, patients who required stenting did worse than those who did not, but this has not been the experience of most investigators. Searching for and treating any underlying anatomic abnormality is stressed to improve outcome.

**CONCLUSIONS**

Current management of acute symptomatic iliofemoral DVT requires timely diagnosis and prompt intervention. Efforts to remove thrombus burden by means of mechanical thrombectomy or thrombolytic therapy is effective in alleviating clinical symptoms, restoring venous patency, and reducing the future risk of postthrombotic syndrome. Although well-designed trials with adequate numbers of patients are generally lacking, the experience described in the literature certainly suggests an improved venous patency and a decreased incidence of postthrombotic syndrome with use of thrombolytic therapy for iliofemoral DVTs. Catheter-directed therapy has been shown to be more effective and appears to be safer than systemic infusion. This treatment modality remains the primary treatment of choice in many clinical practices. Current literature has shown promise with the use of pharmacomechanical thrombectomy in patients with symptomatic iliofemoral DVT.

The case for thrombolysis or pharmacomechanical thrombectomy for iliofemoral venous thrombosis has several grounds for support. The first is that the natural history of iliofemoral venous thrombosis has been clearly shown to have a high incidence of clinically significant chronic venous (Continued on page 79)
clearing clot behind valves, without altering the technique offers potential benefit in prevention of PTS symptoms by rapidly eliminating venous obstruction and preserving valvular function.

The use of the EKOS Lysus System offers a rapid way to initiate thrombolytic therapy for DVT in a busy interventional practice. The ability to quickly place an infusion catheter under fluoroscopic and ultrasound guidance with nontraumatic thrombolyses (performed in usually less than 24 hours) offers a substantial improvement in previous DVT thrombolysis. The lower total dose of thrombolytic drug reduces bleeding and other infusion complications. The absence of mechanical fracturing of the thrombus prevents rare but inadvertent development of pulmonary embolus during the procedure. The new therapy has allowed efficient, safe, and practical thrombolytic therapy for the treatment of DVT in a very time-efficient manner. Additional studies need to be performed to confirm the reduction in postthrombotic syndrome and to convince primary care physicians, emergency department physicians, and others of the importance of referring patients for this therapeutic option.

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