Catheter Directed Thrombolysis for Initial Management of Acute Iliofemoral Deep Venous Thrombosis

Abdulrahman Mohamed Salem[1]& Fouad S Fouad[2]
[1]Department of Vascular Surgery, Ain Shams University
[2]Division of Vascular Surgery, Department of Surgery, Cairo University

ABSTRACT

Aim: *To assess the efficacy of catheter directed thrombolysis in the management of acute iliofemoral deep venous thrombosis and its value as an initial management step.* ***Patients & methods:*** *30 patients with acute iliofemoral deep venous thrombosis without contraindications for thrombolysis managed from April 2013 till April 2016, were included in the study. Patients underwent catheter directed thrombolysis of thrombosed iliofemoral veins within 14 days of occurrence, with or without concomitant stenting. The primary patency of this procedure was assessed and early and late reinterventions were reported.* ***Results:*** *Females were 56.7% (n=17). The anatomic success rate was 100 % (n=30), 1ry stenting was done in 36.6 % (n=11) of cases. The patency rate after 6 months and 1 year was 100 %. One case (3.3 %) of the stented iliac vein needed re-intervention after 18 months. Follow up ranged from 12 to 24 months (mean = 18). CDT was done for the left lower limb in 60% (n=18) of cases. 33 % (n=10) of patients had a hematoma at the site of entry and all were treated conservatively. There was no major systemic bleeding, symptomatic PE or deaths in our study group.* ***Conclusion:*** *Catheter directed thrombolysis is effective and safe and can be implemented as a primary choice in the management of iliofemoral deep venous thrombosis in carefully selected patients.*
Key-words: *Thromolysis, DVT and Phlegmasia*

INTRODUCTION

Deep vein thrombosis (DVT) is a significant cause of morbidity and mortality. Studies have shown that iliofemoral thrombosis is associated with a higher incidence of recurrent DVT and post-thrombotic syndrome. Venous claudication is almost exclusively present in patients with history of iliofemoral DVT. So far, conventional treatment has been limited to anticoagulation and compression therapy alone. However, emerging data suggests that catheter directed thrombolysis (CDT), in combination with appropriate anticoagulation, improves outcome with regard to recurrent DVT, venous obstruction, valve competence, and quality of life. [1]

Catheter-directed thrombolysis (CDT) is increasingly employed for the treatment of selected patients with Iliofemoral Deep Venous Thrombosis (IFDVT), targeting early thrombus removal, maintenance of valvular competence, and reduction of post-thrombotic morbidity and should be considered as first-line therapy in patients with proximal DVT who are at low risk of bleeding. [2]

The overall benefit of thrombolysis depends on multiple factors including: predisposing risks, symptom's 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. [3]

Given the severe morbidity of iliofemoral DVT and the benefits of thrombus removal as demonstrated by natural history studies, observational reports, and randomized trials, appears to be objective evidence supporting a strategy of thrombus removal. [4]

PATIENTS AND METHODS

This is a prospective study which was conducted on patients with Acute Iliofemoral DVT who presented from April 2013 till April 2016. We defined DVT - according to the Quality improvement guidelines published by the Society of Interventional Radiology (SIR) standards of practice committee - as follows:

Acute DVT refers to venous thrombosis for which symptoms have been present for less than 14 days or for which imaging studies indicate that thrombosis occurred within the previous 14 days. Subacute DVT refers to venous thrombosis for which symptoms have been present for 15–28 days as indicated by history or imaging studies. Chronic DVT refers to venous thrombosis for which symptoms have been present for more than 28 days as indicated by history or imaging findings. Acute-on-chronic DVT refers to venous thrombosis that has acute (< 14 d) and nonacute components as indicated by history or imaging findings. [5]

Inclusion Criteria:

1. Patients with iliofemoral DVT proven with duplex.
2. Duration <14 days from the onset of symptoms.
3. Patients who were known to have been mobile and active before the onset of symptoms.
4. Patients with intact pedal pulsations.

Exclusion Criteria:

1. Any contraindication to pharmacologic Catheter-Directed DVT Thrombolysis as mentioned in Table 1.
2. Bed ridden patients.
3. Any advanced malignancy.
4. Previous DVT.

Table 1. Contraindications to Pharmacologic Catheter-Directed DVT Thrombolysis [6]

Absolute contraindications
• Active internal bleeding or disseminated intravascular coagulation
• Recent cerebrovascular event (including TIA), neurosurgery (intracranial, spinal), or intracranial trauma (< 3 months)
• Absolute contraindication to anticoagulation
Relative contraindications
• Recent cardiopulmonary resuscitation, major surgery, obstetrical delivery, organ biopsy, major trauma, or cataract surgery (< 7–10 days)
• Intracranial tumor, other intracranial lesion, or seizure disorder
• Uncontrolled hypertension: systolic BP > 180 mm Hg, diastolic BP > 110 mm Hg
• Recent major gastrointestinal bleeding or internal eye surgery (< 3 months)
• Serious allergic or other reaction to thrombolytic agent, anticoagulant, or contrast media (not controlled by steroid/antihistamine pretreatment)
• Severe thrombocytopenia
• Known right-to-left cardiac or pulmonary shunt or left heart thrombus
• Severe dyspnea or severe acute medical illness precluding safe procedure performance
• Suspicion for infected venous thrombus
• Renal failure (estimated GFR < 60 mL/min)
• Pregnancy or lactation
• Severe hepatic dysfunction
• Bacterial endocarditis
• Diabetic hemorrhagic retinopathy

BP = blood pressure, DVT = deep vein thrombosis, GFR = glomerular filtration rate, TIA = transient ischemic attack.

All procedures were done either in the cath. Lab. or in the operation room (equipped with a mobile C arm with vascular imaging facilities). With the patient in the prone position local infiltration anesthesia is given and duplex guided cannulation of one of the below the knee veins is performed, followed by the introduction of a 6F sheath and a hydrophilic 0.035″ guide wire with a supporting catheter up to the inferior vena cava. After an initial diagnostic cavogram, an infusion catheter (Fountain® Infusion System, Merit Medical Systems Inc.; South Jordan, Utah) with multiple side pores was introduced through the clot followed by injection of a loading dose of recombinant tissue plasminogen activator rTPA (Alteplase) (10 to 15 Units) according to the

thrombus load. After securing the sheath with the infusion catheter in place patients were transferred to an ICU, while being maintained on a continuous infusion of Alteplase (via the catheter with a rate of 0.5 to 2 units per hour according to the thrombus load) and a continuous infusion of unfractionated heparin through the side port of the sheath at a rate of 500 to 1000 units per hour with 6 hourly assessment of PTT with dose modulation to keep it between 80-120 seconds. The patients were monitored for blood pressure, heart rate, bleeding and improvement of symptoms.

Follow up venograms were performed every 12 hours until either restoration of iliofemoral venous flow (anatomic success) or a maximum of 72 hours of therapy. Pre-existing chronic venous lesions unmasked by thrombolysis were treated with placement of a Wallstent® endoprosthesis (Boston Scientific, Inc.; Natick, Mass) which require sheath upsizing that might necessitate a new proximal access site in case of initial PTV or SSV access after cessation of lytic agent for at least 2 hours.

All perioperative complications were recorded including: puncture site hematoma, major bleeding (defined as intracranial bleeding or bleeding severe enough to result in death, surgery, cessation of therapy, or blood transfusion)[6], symptomatic pulmonary embolism and mortality within 30 days of the procedure.

All patients were kept on Warfarin (target INR 2-3) for 6 months. Follow-up visits were scheduled after 6 and 12 months. During each visit, we performed clinical assessment using the Villalta Scale [7] to confirm or exclude PTS and venous duplex to check the patency of treated segments.

The Villalta Scale (Table 2) utilizes the assessment of five patient-rated venous symptoms (pain, cramps, heaviness, paraesthesia and pruritus) and six clinician-rated physical signs (pretibial edema, skin induration, hyperpigmentation, pain during calf compression, venous ectasia and redness). Each sign/symptom is rated as 0 (none), 1 (mild), 2 (moderate), or 3 (severe), and the scores are summed to produce a total score whereby a score < 5 excludes PTS, a score of 5–14 indicates mild/moderate PTS, and a score > 15 or venous ulcer indicates severe PTS.

Table 2: Villalta Scale for the Assesment of PTS

Patient-rated venous symptoms • Pain • Cramps • Heaviness • Paraesthesia • Pruritus **Clinician rated signs** • Pretibial edema • Skin induration • Hyperpigmentation • Pain during calf compression • Venous eclasia • Redness
Each sign/symptom is rated as 0 (none), 1 (mild), 2 (moderate), or 3 (severe), and the scores are summed to produce a total score whereby a score <5 excludes PTS, a score of 5-14 indicates mild/moderate PTS, and a score >15 or venous ulcer indicates severe PTS. PTS – postthrombotic syndrome.

RESULTS

Over a 3-year period 30 patients with unilateral Acute Iliofemoral DVT were treated. The median age was 23 years (16 – 55). 18 of them were females (60%). All patients presented with pain and swelling of the affected limbs 100% but only 5 patients (16.6%) presented with Phlegmasia Cerulea Dolens (massively swollen blue lower extremity). The duration from the onset of symptoms varied from 3 – 14 days with a mean of 10 days. Concomitant inferior vena cava thrombosis was found in 3 cases (10%) while 28 patients (93.4%) had concomitant femropopliteal thrombosis.

Analysis of risk factors revealed: 15 patients were smokers (50%), 4 patients on oral contraceptive pills (13.3%), 7 patients (23.3%) were immobile [2 (6.6%) had a long journey and 5 (16.6%) had a leg cast for recent closed fractures] and 5 (16.6%) turned out to have primary thrombophilia.

Procedural data:

The puncture site was: the ipsilateral popliteal vein in 28 patients 93.3%, the posterior tibial vein in one patient 3.3% and the short saphenous vein in one patient 3.3%. The duration of infusion ranged from 24 to 72 hours. The amount of thrombolytic agent infused ranged from 50–150 units. The infusion rate was 0.5 – 2 units per hour. No IVC filters were inserted.

Completion venograms revealed restoration of iliofemoral venous flow in all patients and that was associated with immediate relief of symptoms. In 11 cases (36.6%) there was a residual structural abnormality after thrombolysis and those patients were treated with a Wallstent® endoprosthesis (Boston Scientific, Inc.; Natick, Mass). The stent diameters ranged from 16 to 18 mm and the lengths from 60 to 90 mm. 10 out of those 11 cases where labeled as "May-Thurner syndrome" and on reviewing their charts they all gave a history of chronic leg swelling.

Limb salvage was possible in the 5 patients who had Phlegmasia Cerulea Dolens (100%). Puncture site hematoma occured in 12 patients (40%) and was treated conservatively without surgical evacuation or blood transfusion. There were no major bleeding events and no clinical evidence of symptomatic pulmonary embolism.

Mean follow-up duration was 18 months (12 – 24 months). At follow-up after 6 and 12 months, the venous system (including the iliac, femoral, and popliteal veins) was examined with duplex US. Iliofemoral patency was defined as regained when the following findings were present: flow in the pelvic and femoral vein, compressibility of the femoral vein, and no functional venous obstruction at any level.

PTS was assessed after 12 months based on the Villalta Scale and 3 patients had mild/ moderate PTS (10%).

Recurrence occurred after 18 months in one case (3.3%) who had a stent placed in his iliac vein when he was treated from his first episode of deep venous thrombosis. We suspect that his stent thrombosed due to non-compliance with oral anticoagulation. This patient was treated successfully with a second attempt of CDT.

Demographic

Female	18	60%
Smokers	15	50%

Risk Factors

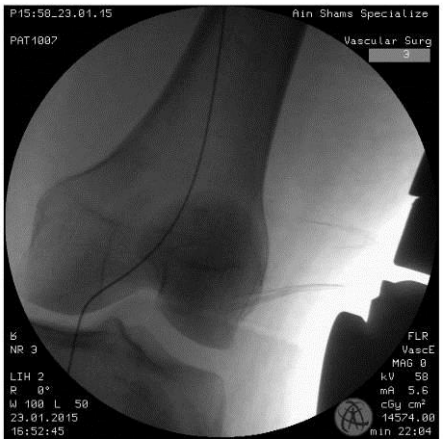
OCP's	4	13.3%
Thrombophilia	5	16.6
Leg cast	5	16.6%
Travelers thrombosis	2	6.6%

OCP's; oral contraceptive pills

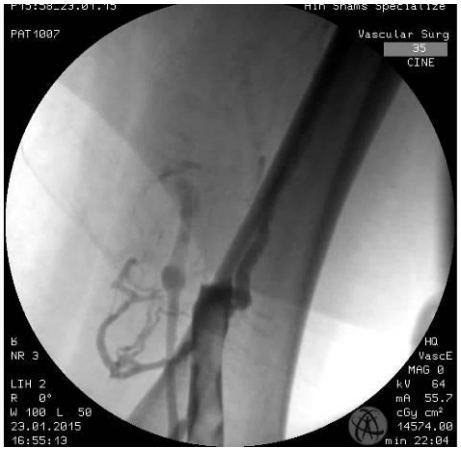
Access Site

PTV puncture	1	3.3%
SSV puncture	1	3.3%
Ipsilateral popliteal vein	28	93.3%

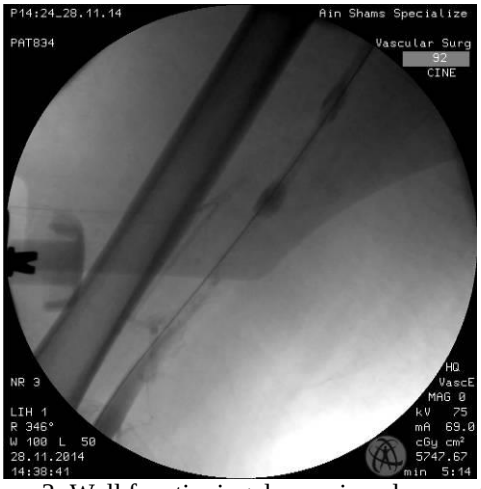
PTV; Posterior tibial vein, SSV; Short saphenous vein,



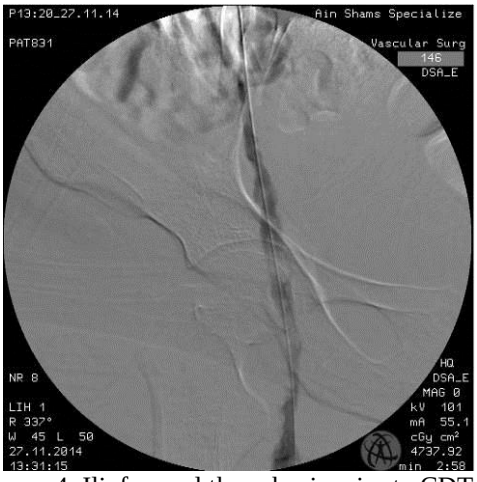
1. Access via ipsilateral popliteal vein



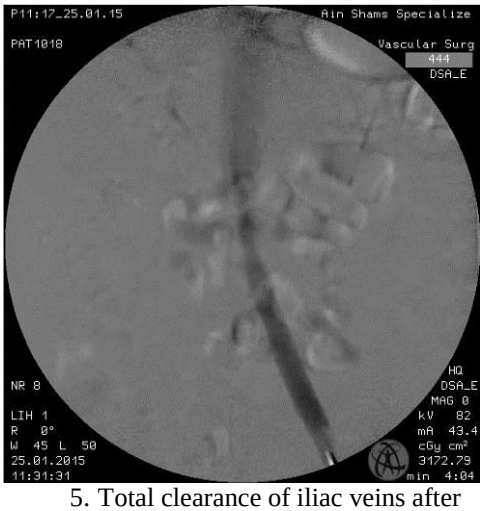
2. Well formed thrombosis of deep veins prior to CDT



3. Well functioning deep vein valves post CDT



4. Iliofemoral thrombosis prior to CDT



5. Total clearance of iliac veins after successful CDT

DISCUSSION

One of the goals in the treatment of DVT is the prevention of the long-term sequelae of the disease, such as PTS, which results from venous occlusion and/ or valvular incompetence caused by DVT. In its most severe form, PTS can lead to debilitating refractory venous ulcers and occasionally venous claudication. PTS not only adversely affects patients' quality of life but also poses a tremendous economic burden to the healthcare system. It is estimated that one of every three patients who experience proximal DVT will have PTS symptoms. [8]

The policy of early removal of the thrombus (percutaneous or open) and preventing valvular damage and chronic occlusion of the deep venous system in cases of iliofemoral DVT has acceptable results regarding long term follow up.[1,4,8]

With the development of endovascular capability and thrombolytic drugs, there are many percutaneous techniques for removal of the thrombus which can be categorized into pharmacological, mechanical and combined (pharmacomechanical) groups. Pharmacological removal of the thrombus is the most commonly used overall but still takes longer time and carries a risk of bleeding both locally and systemically, on the other hand the mechanical removal takes less time and does not involve thrombolytic agents and therefore can be used in patients with a contraindication to lytic therapy. However, it is

more expensive than pharmacological therapy alone.[1]

Current guidelines support CDT as a secondary treatment option for acute proximal DVT but limits this recommendation to patients with iliofemoral DVT, symptoms for <14 days, good functional status, life expectancy over 1 year, and low risk of bleeding.[9, 10]

In our study of carefully selected patients with iliofemoral DVT we used loading and continuous infusion of rTPA (Alteplase).

We limited our study to patients who had acute leg symptoms of less than 14 days duration. Other studies included patients up to 21 days from the onset of their symptoms with non-inferiority results in comparison to early (<14 days) interventions. They just used more Alteplase and required a longer infusion time. [11]

Major bleeding is the most frequent major complication of endovascular DVT thrombus removal and was observed in 2.8% of patients undergoing treatment in randomized trials. [6] In our series there we had no cases of major bleeding.

In a multicenter randomized controlled trial (the CaVenT study) in which 92 patients received infusion-only CDT, there were no cases of procedure-related symptomatic PE. [12] Our series complies with this trial as we also did not have any case of symptomatic PE.

We did not insert an IVC filter in our study. We may consider using it in other patients with proven massive pulmonary embolization or previous pulmonary embolism affecting the patients' cardiopulmonary reserve, but even then, we would insert a retrievable filter. A group from Malmö, Sweden inserted a retrievable IVC filter as a routine step before CDT and they stated that it is not supported by evidence based studies but interestingly enough they found multiple small thrombi in all retrieved filters and large thrombi in some filters after retrieval. They reported no complications during insertion or removal.[11]

However, in other published studies the use of routine insertion of IVC filter was not evidence based and is not recommended as a routine step and should be used selectively as retrievable filters have their own risks.[4]

In reviewing the literature, we found no publication mentioning the use of the SSV as one of access site options. We did use it however in one of our patients. The common access sites (as mentioned in many studies) were: ipsilateral popliteal vein or ipsilateral posterior tibial vein (even if they were loaded with thrombus) and occasionally the ipsi- or contralateral common femoral vein may be used.[12] The limitations for using the ipsilateral SSV are an anomalous saphenopopliteal junction (e.g. an S shaped junction) or lack of communication with the deep venous system when examined by duplex prior to the intervention. In our patient – in whom we used the SSV as an access site - we traced the SSV upwards with duplex and found that it drains directly into the popliteal vein with a normal shaped junction.

Overall (with or without stents) patency rates (immediate and after one year) compare favorably with other studies that defined patency as restoration of iliofemoral venous flow. The standards of practice committee of the society of interventional radiology (SIR) in their review that was published in 2014 selected 30 studies out of 200 articles that reported on the anatomic success after CDT for DVT and they found that most of the studies reported their results as a percentage of the thrombus removed on pre-and post-treatment venograms and that some studies reported their success as restoration of iliofemoral venous flow on venography. [5] We opted to report our results as the latter studies did and while they gave a 91% patency rate ours was 100% immediately after the procedure.

At 12 months, all treated venous segments were found to remain patent by Duplex and that may be explained by our liberal policy in deploying stents in underlying chronic venous lesions. Husmann stated that invasive therapy with catheter-guided thrombolysis and angioplasty without additional stenting results in a high recurrence rate of thrombosis up to 100%.[13]

Stent placement has been reported to facilitate improved rates of venous patency, as evidenced by registry data that indicated higher 12-month venous patency rates for limbs with stents (74%) versus limbs without stents (53%) in patients with iliofemoral DVT who were treated with CDT. [14]

In this study stenting of the iliac veins was done in 11 patients (36.6%) and after 1 year they were all still patent. After 18 months however, we had one stent occlusion which makes our patency rate at that time 91 %. Reported rates of venous patency after stent placement for acute iliofemoral

DVT in May-Thurner syndrome also have been favorable: up to 92% patency at 2 years. [15]

PTS rate after 12 months was 10% and that is much lower than most studies. This could be explained again by the improved patency rate which is known to translate into a reduction in the PTS or the relatively short follow-up duration.

After 24 months of follow-up in the CaVenT study, the incidence of PTS was significantly decreased in patients allocated additional CDT relative to those who received conventional treatment (anticoagulation only).[16]

At the 5-year follow-up point in the CaVenT study, despite favorable results with the use of CDT for prevention of PTS, this therapy failed to improve QOL.[17]

Women more often showed regained patency after 6 and 24 months, but their Villalta score and frequency of PTS did not differ compared with those of men. [12] In our study, however, we could not demonstrate any gender related differences in the outcome.

CONCLUSION

Catheter directed thrombolysis seems to be safe and effective in properly selected individuals who are suffering from acute iliofemoral deep venous thrombosis. Further long-term studies are required to demonstrate that the reduced PTS rate correlates well with an improved quality of life.

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