Short-term patency of catheter-directed thrombolysis for iliofemoral deep vein thrombosis

Mahmoud I. Saleh, Khaled A. Atalla, Ashraf G. Taha, Ahmed K. Sayed

Department of Vascular and Endovascular Surgery, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Ashraf G. Taha, MD, Department of Vascular and Endovascular Surgery, Assiut University Hospitals, 71526 Assiut, Egypt. Tel: +20 100 001 3141; fax: 088 2333327; e-mail: ashraf.g.taha@gmail.com

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Background
Catheter-directed thrombolysis (CDT) for the treatment of acute iliofemoral deep venous thrombosis (IFDVT) has the advantages of prompt thrombus removal, restoration of the vein patency, and maintenance of the valve function. It also facilitates endovascular treatment of the commonly-encountered vein lesions. Therefore, the aim of the study is to assess the efficacy, safety, short-term patency rates, and incidence of post-thrombotic syndrome (PTS) following CDT treatment of IFDVT.

Patients and methods
This is a prospective study of all adult patients who underwent CDT for the treatment of acute, nonrecurrent, radiologically proven IFDVT at the Department of Vascular and Endovascular Surgery, Assiut University Hospital (a tertiary referral hospital), between June 2015 and November 2016.

Results
Sixty-four patients (64 limbs) underwent CDT for treatment of acute IFDVT. The overall success rate was 93.8%. Balloon angioplasty was performed in 58 (96.7%) patients, of which, 54 (90%) required stent placement. Eight (12.5%) bleeding complications were encountered in the study, with only one major bleeding event. No periprocedural cerebral hemorrhage, pulmonary embolism, or deaths occurred. At 1 year, the cumulative primary patency rate was 76.5%. Seven (12.1%) patients had symptoms of PTS (four mild, two moderate, and one severe) without occurrence of venous ulceration in any patient.

Conclusion
CDT is a safe and effective treatment option for patients with acute IFDVT, with satisfactory technical success and acceptable short-term primary patency rates. Prompt thrombus lysis associated with adjunctive treatment of vein lesions can help reduce rate of rethrombosis and the subsequent development of PTS.

Keywords:
catheter-directed thrombolysis, deep venous thrombosis, post-thrombotic syndrome, vein stenting, venous patency

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Introduction

Iliofemoral deep vein thrombosis (IFDVT) can lead to a significant morbidity in the short term [acute pulmonary embolism (PE)] and the long term, including post-thrombotic syndrome (PTS) [1], and increased rates of thrombosis recurrence [2]. The conventional treatment of deep venous thrombosis (DVT) using anticoagulation therapy can effectively decrease thrombus extension, recurrence, and incidence of PE [3]. Nevertheless, anticoagulation alone does not dissolve the thrombus, which may cause valvular reflux and/or venous obstruction [4,5] with subsequent development of PTS in up to 50% of patients with IFDVT [6–8]. The typical manifestations of PTS include leg pain, edema, pigmentation, and venous ulceration [9], representing a great effect on patients' quality of life and increased economic burden on the patient and the society [10].

Catheter-directed thrombolysis (CDT) has become the recommended technique for the treatment of proximal DVT, where the thrombolytic agent is directly delivered into the thrombus through a catheter imbedded in the thrombosed venous channels [11]. Using this method, previous studies have reported satisfactory success rates with reduced rates of procedural complications, thrombosis recurrence, and development PTS [12,13]. However, the most recent trial comparing the incidence of PTS in patients with DVT treated with pharmacomechanical CDT versus anticoagulation alone did not show a significant difference between the two treatment groups [14]. Consequently, more studies are still needed for further assessment of CDT in the treatment of IFDVT including analysis of frequency and severity of subsequent PTS. Therefore, the aim of the study is to assess the efficacy, safety,

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short-term patency, and incidence of PTS following CDT treatment of IFDVT.

Patients and methods

Study setting

This is a prospective study of all adult patients who underwent CDT for the treatment of acute nonrecurrent IFDVT at the Department of Vascular and Endovascular Surgery, Assiut University Hospital (a tertiary referral hospital), between June 2015 and November 2016.

Patients

All patients with symptoms of acute IFDVT were confirmed by duplex ultrasonography examination and computed tomography venography before starting CDT. The study excluded patients who were 18 years old or younger, those who had onset of symptoms of 21 days or longer, and patients with recurrent ipsilateral DVT. Patients with bleeding diathesis, malignancy, pregnancy, severe hypertension, or contraindication to thrombolytic therapy were excluded from CDT.

Laboratory tests of thrombophilia, including protein C, protein S, and antithrombin assays, were done for young patients or those with unprovoked DVT. Informed consent was taken from all patients after explanation of all risks and benefits of the treatment procedure.

Procedure technique

According to our protocol, vein access is done at the hybrid operating room under local infiltration anesthesia. The ipsilateral popliteal vein (PV) is our typical access vein, irrespective of concomitant thrombosis. While the patient is in prone position, the PV is punctured under ultrasound guidance, followed by placement of a 6-Fr vascular sheath. Alternatively, the posterior tibial vein or short saphenous vein at the ankle was used if the PV was difficult to access.

Diagnostic venography is done to confirm the upper limit of the thrombus. A hydrophilic guide wire and catheter are advanced through the thrombus till reaching the inferior vena cava (IVC). Oblique projections are necessary to help crossing the iliac lesion and to confirm adequate positioning of the guide wire in the IVC rather than the paravertebral veins. Imaging of the IVC was performed in all CDT procedures. Prophylactic IVC filter placement was not required in any of our study patients.

After crossing the thrombosed segment, a multiple side-hole infusion catheter (Uni*Fuse; Angiodynamics, Latham, New York, USA) with an infusion length of 20–50 cm is placed to cover the entire length of the thrombus. Thrombolysis is then started using alteplase (Actilyse; Boehringer-Ingelheim, Ingelheim am Rhein, Germany). Alteplase (50 mg diluted in 500 ml 0.9% NaCl solution) is infused at rate of 1 mg/h. For prevention of thrombosis around the access, continuous infusion of unfractionated heparin through the introducer sheath is done at a rate of 300–500 U/h to keep activated partial thromboplastin time 1.2–1.7 higher than normal.

The patient is transferred to the ICU for close observation of the vital signs and the puncture site for external bleeding or hematoma formation. Laboratory monitoring of lysis therapy includes activated partial thromboplastin time, fibrinogen level, and complete blood picture. Lysis check is done every 24 h at the hybrid operating room to evaluate thrombus response to CDT.

Thrombolysis is terminated when the maximum benefit of CDT is achieved, defined as complete thrombus lysis or lacking of lysis progress after the initial 48 h of CDT. The procedure must be stopped after 96 h of CDT, reaching the maximum dose of alteplase (20 mg/24 h), or with occurrence of severe complications such as major bleeding or PE.

After clot lysis, any detected significant venous lesions are corrected by balloon angioplasty and selective stenting if the residual stenosis is 50% or more (Fig. 1). For venous stenotic lesions, we use high-pressure balloon angioplasty catheters (diameter: 12–16 mm, length: 40–100 mm, Atlas; Bard Peripheral Vascular Inc., Tempe, Arizona, USA). Stents used were either WallStent (Boston Scientific, Marlborough, Massachusetts, USA) or Zilver Vena (Cook Medical Inc., Bloomington, Indiana, USA) with diameters of 14–18 mm and length of 70–140 mm.

Postoperative care

Following CDT, subcutaneous low-molecular-weight heparin is administered at a therapeutic dose. Warfarin is started before patient's discharge to maintain an international normalized ratio from 2 to 3 for at least 1 year. Patients who received venous stenting were given dual antiplatelet therapy for 1 month postoperatively. All patients are instructed for daily wear of a class-2 compression stocking for 2 years.

Technical assessment

Outcome assessment of CDT is categorized into one of three grades according to amount of thrombus lysed at the end of the procedure. Consequently,

grade 1 (no or minimal lysis), grade 2 (partial lysis), and grade 3 (complete lysis) represent the percentage of thrombus removal by less than 50%, 50–90%, and more than 90%, respectively. Technical success is defined as achievement of grade 2 or grade 3 lysis at the end of the CDT procedure and at 1 month postoperatively.

Follow-up

Follow-up visits for clinical and DU examinations are typically scheduled at the outpatient clinic at 1, 3, 6, and 12 months, postoperatively. Recurrent DVT was defined by appearance of recurrent symptoms and confirmed by DU examination. Primary patency is defined as the time interval from the end of the CDT procedure till the occurrence of ipsilateral rethrombosis. Villalta scale was used for diagnosis of PTS; a total score of more than 5 indicates occurrence of PTS [15]. The degree of PTS was classified as mild, moderate, and severe if the scores were 5–9, 10–14, and more than 15, respectively. Appearance of venous ulcer is a definite sign of severe PTS.

End points

The primary end points are the patency of iliofemoral vein segment and frequency of PTS at 12 months. Periprocedural complications were the secondary end points of the present study.

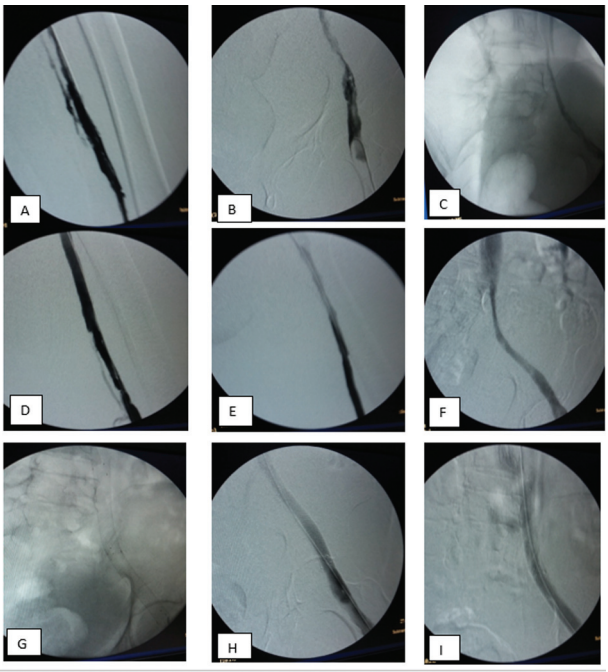
Statistical analysis

Statistical analysis was performed using SPSS 24.0 (SPSS Inc., Chicago, Illinois, USA), and MedCalc 16.8 (MedCalc Software, Ostend, Belgium). Descriptive statistics were used, with continuous variables expressed as mean±SD and categorical variables as frequencies and percentages. Kaplan–Meier analysis was used to estimate cumulative primary patency rates. Survival rates were reported as proportion, and intergroup differences were compared using the log-rank test. A value of P less than 0.05 was considered statistically significant.

Results

Between June 2015 and November 2016, 64 patients (64 limbs) underwent CDT for treatment of acute IFDVT with or without distal propagation. Concomitant IVC thrombosis was present in two patients. All patients presented with unilateral disease, with the left lower limb more commonly affected (68.7%). Mean duration of symptoms was 6.6 days (SD: 4.4, range: 1–19 days). Baseline characteristics for study patients are shown in Table 1.

Figure 1



(a–i): Popliteal venogram showing acute iliofemoral deep venous thrombosis with extensive filling defects at the femoral (a), external (b), and common iliac veins (c). (d–f) Post-catheter-directed thrombolysis venograms showing complete thrombus lysis with significant stenosis at the common and external iliac veins. (g–i) Final venogram showing stenting of the common and the external iliac veins with restoration of flow into femoral and iliac veins and the inferior vena cava.

Table 1 Baseline characteristics of the study patients

Variables	
Age (years)	
Mean±SD	45.2±3.7
Range	22–70
Sex [*n* (%)]	
Male	23 (35.9)
Female	41 (64.1)
Side [*n* (%)]	
Right	20 (31.3)
Left	44 (68.7)
Duration [*n* (%)] (days)	
≤14	48 (75)
15–21	16 (25)

Outcome of thrombolysis

Procedural details and risk factors for DVT are shown in Table 2. The overall success rate (grade 2 and grade 3 lysis) was 93.75% (n=60), with a complete lysis achieved in 33 (51.6%) patients. CDT failed in four (6.25%) patients; three had grade 1 (<50%) lysis, whereas one patient had the procedure terminated after development of large thigh hematoma.

Adjunctive endovascular treatment was required in 58 patients (of the 60 successfully lysed patients) to correct the underlying lesions unmasked by the CDT. Balloon angioplasty was performed in 58 (96.7%) patients, of

Table 2 Procedural details and etiology/risk factors for deep venous thrombosis

Procedural details	*n* (%)
Access vein	
Popliteal vein	53 (82.8)
Posterior tibial vein	8 (12.5)
Small saphenous vein	3 (4.7)
Dose of alteplase (mean±SD) (mg)	49.2±7.4
Lysis duration (mean±SD) (h)	53.5±1.3
Technical outcome	
Failed lysis	4 (6.25)
Procedure termination	1 (1.56)
Grade-1 (<50% lysis)	3 (4.69)
Successful lysis	60 (93.75)
Grade-2 (50–90% lysis)	27 (42.2)
Grade-3 (>90% lysis)	33 (51.6)
Adjuvant endovascular procedures	
Not needed	2/60
PTA only	4/60
PTA and stenting	54/60
Etiology/risk factor for DVT	
May–Thurner syndrome	39
Hypercoagulability	6
Prolonged immobilization	3
Postoperative	3
Postpartum	4
Contraceptive pills	3
Unknown	6

DVT, deep venous thrombosis; PTA, percutaneous transluminal angioplasty.

which, 54 (90%) required stent placement. Forty-four patients required one stent placement whereas eight patients had two stents. The two patients with IVC lesions required IVC stenting in a double-barrel fashion, with a total number of stents of four and six in either patient.

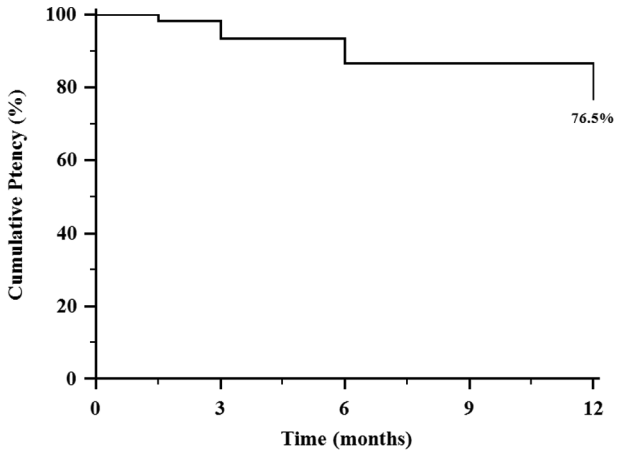
Complications

Eight (12.5%) bleeding complications were encountered in the study patients, with only one major bleeding event. This was a thigh hematoma which necessitated blood transfusion, thigh fasciotomy, and termination of the procedure. This complication was attributed to a recent intramuscular injection before CDT. Other complications included hematuria in three patients, access site hematoma in two patients, and bleeding via vagina in two patients. No periprocedural cerebral hemorrhage, PE, or deaths were encountered in the study.

Follow-up

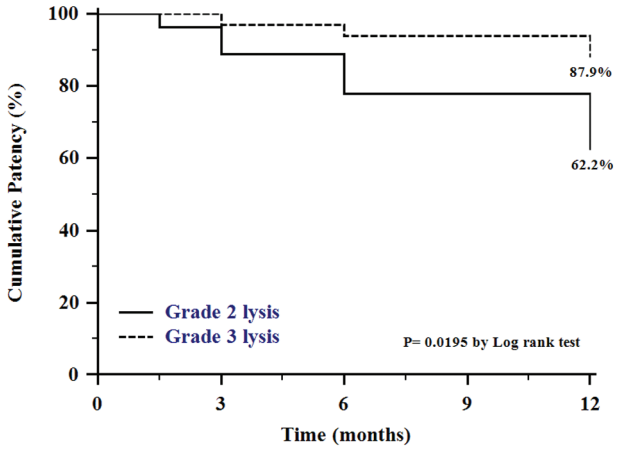
Of the successfully treated 60 patients, 58 completed the 12-month follow-up, with a cumulative 1-year primary patency rate of 76.5% (Fig. 2). Subgroup analysis (Fig. 3) showed a significant difference in the 1-year primary patency rates between patients

Figure 2



Kaplan–Meier survival curve demonstrating primary patency rate at 1 year after successful catheter-directed thrombolysis of iliofemoral deep vein thrombosis.

Figure 3



Kaplan–Meier survival curve demonstrating primary patency rate at 1 year after complete versus partial catheter-directed thrombolysis of iliofemoral deep vein thrombosis.

with complete (87.9%) versus partial (62.2%) lysis (P=0.019), indicating the relationship between the amount of post-CDT residual thrombus and the risk for rethrombosis. After 1 year, seven (12.1%) patients developed symptoms of PTS (four mild, two moderate, and one severe) without occurrence of venous ulceration in any patient.

Discussion

The current treatment modalities for IFDVT are anticoagulation alone, systemic thrombolysis, CDT, percutaneous mechanical thrombectomy, and surgical thrombectomy. For many years, anticoagulation therapy alone was the treatment of choice for DVT. However, the high rates of subsequent PTS and venous ulcers, especially with IFDVT, mandated seeking

other treatment options targeting thrombus removal and restoration of vein patency [6,7]. Systemic thrombolysis, however, has been associated with serious bleeding events [16,17]. The invasive nature of surgical venous thrombectomy and the requirement of anesthesia significantly limited the use of this treatment option [18]. Using CDT to locally deliver a thrombolytic therapy to lyse the thrombus, protect valve function, and maintain venous patency seemed a reasonable option. The reported decreased incidence of recurrent thrombosis and PTS after CDT made it the preferred modality for treatment of IFDVT [12].

The present study showed a success rate of CDT of 93.8%, with a complete lysis achieved in 33 (51.6%) patients, which is comparable to those reported by previous studies [19–23]. Of the four failures of CDT, three were because of a minimal lysis despite careful commitment to the technical steps. It is well known that duration of DVT symptoms is closely related to the success of CDT procedure. Chronicity of symptoms means more aged thrombus with an inherent probability for decreased procedural success. The two big randomized trials, the CaVenT [24] and the ATTRACT [25], have adopted 21 and 14 days, respectively, as cutoff points for performing CDT in patients with DVT. In our study, CDT was not used if the patient-reported onset of symptoms lasted more than 21 days. The inaccurate reporting of the onset of symptoms, oftentimes given by the patient, may partly explain the weak response of the lysis treatment with vein thrombosis lasting more than 21 days.

Another fundamental benefit of using CDT is detection of the underlying venous outflow lesion after thrombus removal. Using the interventional therapy facilitates the correction of the unmasked culprit lesion by angioplasty and stenting during the same procedure. Conventional treatment by anticoagulation alone does not offer this advantage, and therefore, the rate of recurrence may be increased [11].

Iliac vein lesions are believed to be a common etiology of IFDVT with incidence rates of thrombosis reaching to 72% [26]. Extrinsic compression of the iliac vein by the iliac artery (May–Thurner syndrome) is a common cause of iliac vein disease [26]. In the present study, 39 (65%) patients were found to have May–Thurner syndrome that required stent placement to ensure an unconstrained venous outflow. In a study of 155 patients with DVT treated with CDT, Meng *et al.* [27] found 74 (48%) patients with iliac vein lesions; 45 were treated by stent placement, resulting in better a 1-year patency rate compared with the nonstented group.

Patients with chronic obstructive lesions of the IVC are associated with different clinical presentations, including acute DVT with often presentation at one limb only [28]. In the two patients with IVC lesions, stenting of the IVC was mandatory to restore the vein patency. Both patients were proved to have thrombophilia without any source of vein compression.

Our 1-year primary patency rate was 76.5% which is comparable to those reported by other studies [20,29–31]. Other authors also reported satisfactory long-term primary patency rates (82% at 6 years) after CDT of IFDVT [13]. The relationship between the amount of residual thrombus and patency rates has been studied in few series [32,33]. Park *et al.* [34] reported higher 3-year patency rates in patients with complete lysis (75%) compared with those with partial lysis (30%, P=0.03). In the present study, 1-year patency rates were significantly higher after complete lysis compared with partial lysis (88 vs. 62%, P=0.019).

As recommended in several studies, we used Villalta score for a reliable diagnosis and assessment of PTS severity [15,35]. PTS can develop at any time after occurrence of DVT, more commonly in patients with IFDVT, with at least 60% of cases will occur within 2–3 years [13]. The syndrome results from valvular reflux and/or residual obstruction in response to acute DVT. Therefore, early thrombus removal can preserve valve function and prevent occurrence of PTS [9,12].

At 1 year, only seven (15.2%) of our patients developed PTS, with only one patient with severe symptoms. Venous ulceration was not encountered in any of the study patients. In a study by Yang *et al.* [1] on patients with lower extremity DVT, the 12-month incidence of PTS after CDT was 18%, which was significantly lower than its incidence (52%) in patients treated by conventional anticoagulation treatment. Similarly, the CaVenT study reported an absolute risk reduction of 14.4% of PTS occurrence after CDT compared with patients received anticoagulation alone [36]. Although the ATTRACT study did not report a lowered risk for all-severity PTS in CDT-treated patients compared with those treated with oral anticoagulation only, their incidence of moderate-to-severe PTS was significantly lower in the CDT group (18 vs. 24%; P=0.04) [14]. Incidence of PTS in our study comes in line with rates reported in other series [13,34], indicating that CDT can be an effective treatment in reducing the incidence and severity of PTS after DVT insult.

Hemorrhage is known to be the main complication related to CDT [1,12]. Bleeding rate in our study was 12.5%, with only one major bleeding event. Similar rates of minor and major bleeding were reported in other series [29,36]. Hematuria and puncture site hematoma were the most common complications in our study. No cerebral hemorrhage, PE, or deaths occurred in our patients. Careful patient selection and strict laboratory monitoring before and during CDT can greatly help reduce the risk of bleeding during CDT procedures.

Study limitations

There are some limitations in the present study including the small sample size, no control patients treated with anticoagulation alone, lack of patients' history records to confirm absence of previous attacks of ipsilateral DVT, and lack of long-term follow-up of the treated patients.

Conclusion

CDT is a safe and effective treatment option for patients with acute IFDVT, with satisfactory technical success rates and acceptable short-term primary patency rates. Prompt thrombus lysis associated with adjunctive treatment of vein lesions can help reduce rate of rethrombosis and the subsequent development of symptoms of PTS.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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