Acute iliofemoral deep vein thrombosis: does catheter-directed thrombolysis affect outcomes?

El-Sayed A. Abd El-Mabood[a,b], Waleed A. Sorour[c]

[a]Departments of General and Vascular Surgery, Benha University, [b]Department of Vascular Surgery, Benha Insurance Hospitals, Benha, [c]Department of Vascular Surgery, Zagazig University, Zagazig, Egypt

Correspondence to El-Sayed A. Abd El-Mabood, MD, Department of Surgery, Benha University Hospitals, Borg, Tiba Misr Beside Elfath School Elfell, Benha, Kaliobia, Benha 13516, Egypt. Mob: 01065351802; E-mail: elsayedafifi@yahoo.com

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Purpose
The aim was to assess the role of catheter-directed thrombolysis (CDT) in improving patency of the treated venous segments and to examine the correlation of residual thrombus with post-thrombotic syndrome (PTS).

Background
Iliofemoral deep vein thrombosis (DVT) is associated with severe post-thrombotic morbidity when treated with anticoagulation alone. CDT allows early removal of thrombus and reduce valvular reflux and PTS.

Patients and methods
This prospective randomized controlled two-arm study was conducted on 42 patients with iliofemoral DVT. The patients were randomly allocated into two groups according to the intervention performed. Group A: CDT followed by oral anticoagulants [*N*=21 (50%)], group B: standard DVT therapy [*N*=21 (50%)]. The follow-up period was 24 months.

Results
Patients of group A complained of less pain at 10 and 30 days (*P*=0.02 and 0.04, respectively). Also, there was significant decrease in leg circumference in group A at 10 and 30 days (*P*=0.001 and 0.03, respectively). A total of three (15%) clinically relevant nonmajor bleeding complications were reported in the CDT group. Using CDT is associated with less PTS at sixth month, 1 year, and 2 years; six (27.3%), seven (31.8%), and nine (40.9%), respectively, as compared with group B; 11 (47.8%), 13 (56.5%), and 15 (65.2%), respectively (*P*=0.024, 0.017, and 0.035, respectively).

Conclusion
Addition of CDT in the treatment of acute iliofemoral DVT was safe and tolerated by most of the patients with better effect to reduce leg pain and circumference. It was considered a protecting weapon to prevent PTS and thereby improving the quality of life and was related to achievement of higher iliac vein patency and less reflux.

Keywords:
catheter-directed thrombolysis, iliofemoral venous thrombosis, post-thrombotic syndrome, standard anticoagulation

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Introduction

Acute deep venous thrombosis (DVT) range from asymptomatic calf vein thrombosis to painful, blue, swollen limb of phlegmasia cerulea dolens due to extensive multisegment thrombosis including iliofemoral venous segment [1].

Deep venous thrombosis of the lower extremity is the cause of both pulmonary embolism and post-thrombotic syndrome (PTS). Therapeutic goals include diminishing the severity and duration of lower extremity symptoms, preventing pulmonary embolism and preventing PTS sequelae [2,3].

PTS is a debilitating condition that diminishes the quality of life and often worsens over time. Post-thrombotic venous disease is due to ambulatory venous hypertension, which is defined as elevated venous pressure during exercise that may lead to swelling, pigmentation, lipodermatosclerosis, and microcirculatory changes leading to dermal breakdown [1,4].

Anatomic components causing ambulatory venous hypertension are venous valvular incompetence and luminal obstruction. The most severe post-thrombotic morbidity is associated with the highest venous pressures, which occur in patients with both valvular incompetence and luminal venous obstruction [1,5].

The most severe post-thrombotic morbidity is found in patients who have had thrombosis of their iliofemoral venous segment. Additionally, the risk of recurrent

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venous thromboembolism for patients with iliofemoral DVT is significantly higher than patients with infrainguinal DVT [6–8].

There are strategies for early thrombus removal; operative venous thrombectomy is not adopted by many vascular surgeons, except for patients who are not candidates for catheter-directed thrombolysis (CDT) or when CDT is not available [1,9].

Systemic thrombolysis has limitations of being associated with higher risks of bleeding and failure in patients with extensive occlusive venous thrombosis. CDT has emerged as an alternative endovenous treatment for DVT, and is now the preferred method of management of iliofemoral DVT if thrombus removal is desired [9,10].

Standard anticoagulant therapy aims at the prevention of PE and recurrent DVT. However, more than 50% of patients with proximal DVT may suffer from PTS within the first 1–2 years. Severe PTS occurs in 5–10% of all symptomatic DVTs, and may lead to venous ulceration. Patients with PTS have a poorer quality of life than patients with chronic lung disease, diabetes, or arthritis, and those with severe form of PTS have a quality of life comparable to that of patients with congestive heart failure or cancer [8].

CDT can be done either ultrasound assisted or conventional catheter-directed, that is, fluoroscopic guided and is the favored route of administration in recent years for preserving venous function, and patient selection is important to reduce the risk of complications [11,12].

The basic mechanism of thrombolysis is activation of fibrin-bound plasminogen and production of plasmin. Local delivery of plasminogen activator is more effective and potentially safer than systemic infusion. Additionally, intrathrombus delivery protects plasminogen activators from circulating plasminogen activator inhibitor and protects active enzyme plasmin from neutralization by circulating antiplasmin. This neutralization of circulating plasminogen is so effective that the half-life of plasmin in the systemic circulation is only a fraction of a second [1].

Patients and methods

The patients were included after approval by the Local Ethics Committee of Benha and Zagazig Universities and Benha Insurance Hospitals and obtaining fully informed patients written consent. Patients with iliofemoral DVT were enrolled at these three clinical centers from November 2015 till October 2019; the enrollment period was 24 months and the patient follow-up period was 24 months.

This prospective multicenter randomized controlled two-arm interventional study was conducted on 42 patients with iliofemoral DVT. Patients were randomly allocated by using the simple random allocation method, where 42 cards (21 were signed as group A and other 21 were signed as group B) were prepared by the principal investigator and were put in closed envelops and mixed together. Each patient has chosen an envelope after he had approved for participation. MedCalc software version 16.1 (1993–2016 MedCalc Software, Ostend, Belgium; http://www.medcalc.org; 2016) was used. Level of significance (type I error)=0.05, type II error (1-level of power)=0.1. Null hypothesis percentage=50%.

Patients included in this study were aged 20–60 years. Onset of symptoms within 14 days and iliofemoral DVT with open distal part of the popliteal vein was verified by a duplex scan. The patients excluded from this study were those suffering from bleeding diathesis with hemoglobin less than 8 g/dl and/or thrombocytopenia (platelets $<80\,000/mm^3$), renal impairment (estimated creatinine clearance <30 ml/min), acute DVT during pregnancy or within 7 days postpartum or within 14 days following major surgery or trauma, history of recent subarachnoid, intracerebral or gastrointestinal tract bleeding, drug abuse or mental disease that could interfere with treatment and follow-up, recurrent iliofemoral DVT, aplasia of inferior vena cava (IVC), or current malignant disease.

All patients presenting were admitted at the Vascular Unit, General Surgery Ward for clinical evaluation, routine hematological tests, and venous duplex of both lower limbs; after this, the patient was posted for intervention.

Group A of catheter-directed thrombolysis

In the prone position, 10 ml of 2% lignocaine was injected subcutaneously and under ultrasound guidance, a 19 G 10 cm needle was used to puncture the popliteal vein followed by advancing a 6-French standard sheath. Venography was then performed. A 0.035-inch 260 cm j-tip hydrophilic guidewire (standard type of ZIP wire (Boston Scientific, Chaska, Minnesota, Washington, USA) was used to cross the thrombus to a healthy part of the IVC. When difficulty was encountered during crossing of the

lesion, a stiff type of ZIP wire of 0.035 inch 270 cm (Boston Scientific) was used.

After adequate flushing with heparinized saline, a 5-French 135 cm length Uni Fuse catheter (Angiodynamics Inc., Queensbury, New York, USA) with an infusion segment length of 40 or 50 cm according to the length affected was advanced over the guidewire. The guidewire was exchanged for the occluding wire which was intended to occlude the end hole of the catheter; therefore, the infused thrombolytic agent exited the catheter only through its side holes (inside the thrombus). Correct placement of the catheter and occluding wire were checked radiographically.

Then thrombolytic therapy, that is Alteplase (Actilyse; Boehringer-Ingelheim, Ingelheim am Rhein, Germany); 50 mg (two bottles, one powder and another solution at a 50 : 10 ml loading dose was injected followed by flush saline and then the patient was transferred to the intermediate care unit where 0.01–0.05 mg/kg/h maintenance dose (1 ml/h till 40 h) by the squirt pump with heparin ampoule IV every 4–6 h or continuous infusion 500 IU/h using a syringe pump; then imaging and managing according to findings.

A venogram was then performed to determine the need for venoplasty, and/or venous stents for culprit lesions of greater than 50% narrowing. At the end of the procedure, infusion catheter and sheath were removed and followed by manual compression for 20 min and then crepe bandage was applied for further 2 h. Low molecular weight heparin (LMWH) (enoxaparin 1 mg/kg/12 h) was started 2 h after removal of the sheath. Warfarin was started the second day postprocedure. Anticoagulation was then continued as mentioned in group B. Patients were discharged home whenever there was neither hematoma nor any suspicion of concealed hemorrhage and after initiation of warfarin therapy. Patients were advised to wear fit-sized above-knee, 30–40 mmHg, graduated elastic compression stockings at the 10-day follow-up visit for 2 years (BELSANA, Bamberg, Germany).

Group B of standard anticoagulation

Patients were prescribed anticoagulant therapy in accordance with local routines based on international guidelines using the LMWH enoxaparin (Clexan; Sanofi, Zeiton, Cairo, Egypt) at a dose of 1 mg/kg/12 h, for at least 5 days. Oral warfarin (Marven; GlaxoSmithKline, New Cairo, Cairo, Egypt) was started the day of randomization, at a daily dose of 5 mg. The dose was modified according to the patient's international normalized ratio (INR) with a target INR of 2.0–3.0. LMWH was stopped when the patient's INR is 2.0 or above for at least 24 h. Warfarin was continued for at least 3 months. Patients were advised to wear fit-sized above-knee, 30–40 mmHg, graduated elastic compression stockings at the 10th day visit for 2 years (BELSANA medical).

Follow-up

Patients were returned for follow-up monthly for 24 months postrandomization. At each visit, the patient was evaluated for signs and symptoms of DVT and/or PE and PTS. Because PTS varies in its clinical manifestations, its presence and severity were evaluated in complementary ways. Villalta score was recorded to assess for the development of PTS. The occurrence of PTS was counted if the Villalta score at that visit was 5 or higher. This score consists of five venous symptoms (pain, paraesthesia, pruritis, cramps, and heaviness) and six physical signs (pretibial edema, skin induration, redness, hyperpigmentation, venous ectasia, and calf tenderness), which are rated on a four-point scale, whereas 0=none, 1=mild, 2=moderate, and 3=severe. Points are summed to produce score (0–33). Patients were classified as having mild PTS, when the Villalta score was 5–9; moderate PTS, when the Villalta score was 10–14; and severe PTS, when the score was greater than or equal to 15 or when there is presence of venous ulcer.

All patients were subjected to a venous duplex examination of the treated venous segments at 1, 6, 12, and 24 months postprocedure and at any time a suspicion for PTS and DVT was raised. Recurrent DVT was considered if the previously compressible vein segment became noncompressible or there was greater than 5 mm increase in diameter of the thrombus on ultrasound evaluation. PE was suspected when symptoms of dyspnea, chest pain, cough, fever, hemoptysis, and/or syncope have occurred and diagnosis was supported by multislice computed tomography (CT) pulmonary angiography or/and echocardiography. Also venous duplex was used for detection of post-thrombotic iliofemoral wall thickening and residual thrombi and to evaluate iliofemoral venous flow and reflux. Venous reflux was defined as reversal of velocity curve lasting greater than 0.5 s after distal compression while the patient was in standing position.

Patient-reported health-related quality of life at admission and 24 months was assessed with the use of the venous disease-specific Venous Insufficiency Epidemiological and Economic Study Quality of

Life (VEINES-QOL) measure; this measure includes symptom-specific score that ranges from 0 to 100, with higher scores indicating better quality of life. A difference of three to four points is considered clinically meaningful [13]. Leg pain and leg swelling at first day, 10 days, and 30 days were assessed. Pain was evaluated using a visual analog score. Patients in both groups ranked the level of pain from 0 (no pain) to 10 (very severe pain). But leg swelling was evaluated by measuring calf circumference at 10 cm below the tibial tuberosity.

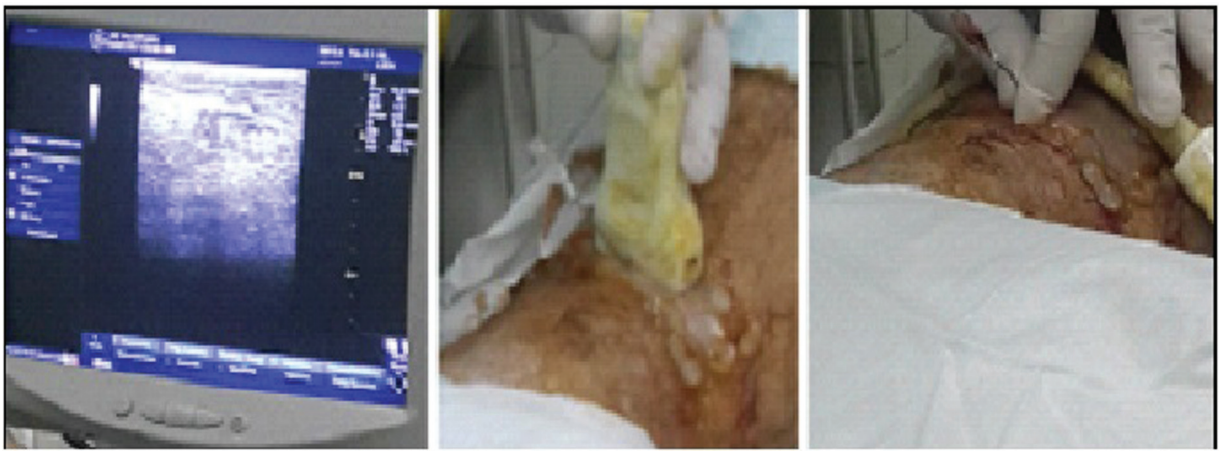
Statistical analysis

Collected data were tabulated and analyzed using SPSS version 16 software (SPSS Inc., Chicago, Illinois, USA) and MicroStat W software (India, CNET Download.com). Categorical data were presented as number and percentages, using χ^2-test or Z-test of two proportions ($Z_{PROP.}$) for their analysis. Continuous data were expressed as mean±SD. Data were tested for normality using Shapiro–Wilks test, assuming normality at P greater than 0.05. Differences between groups were tested using Student's 't' for normally distributed variables or Mann–Whitney U (Z_{MWU}) test for nonparametric ones. Accepted level of significance was stated at 0.05 ($P \leq 0.05$ was considered significant) [14]. Sample size was calculated with a power of 90% with a marginal error of 5%.

The companies mentioned in this study played no role in the design or conduct of the trial or in the analysis or reporting of the data. All scores in this study were recorded by independent investigators and statistician.

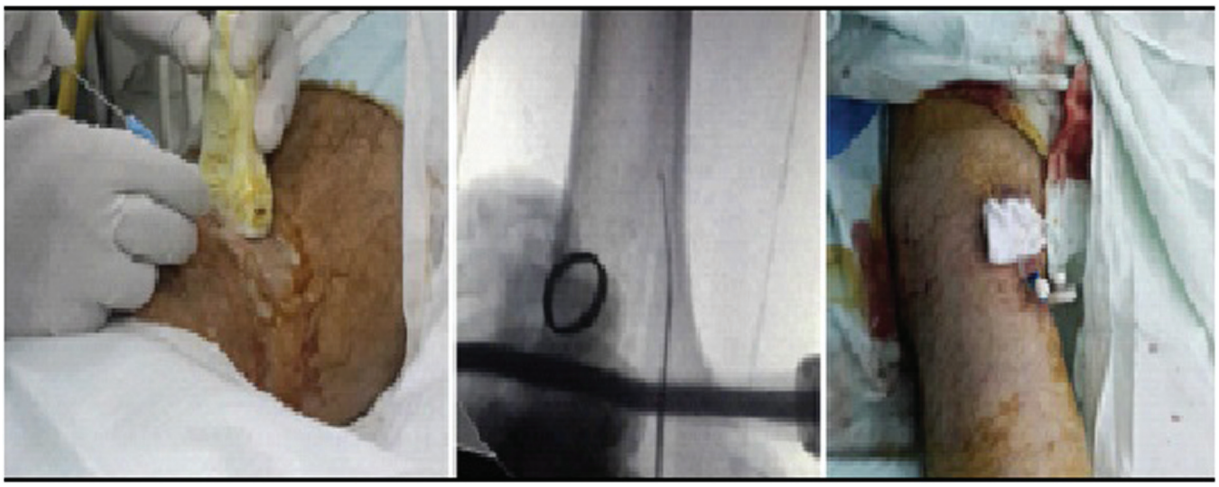
These all data are shown in the following pictures (Figs 1–4).

Figure 1



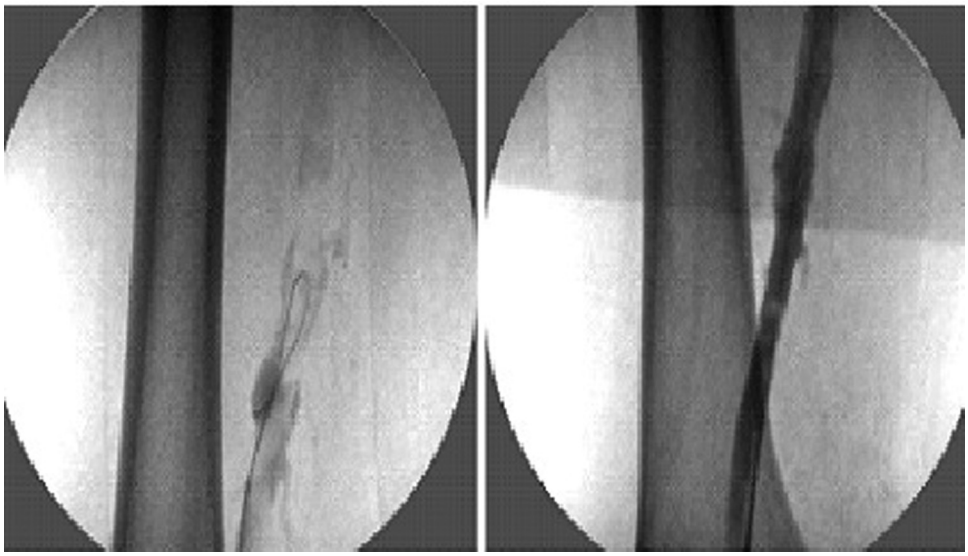
Duplex-guided needle insertion.

Figure 2



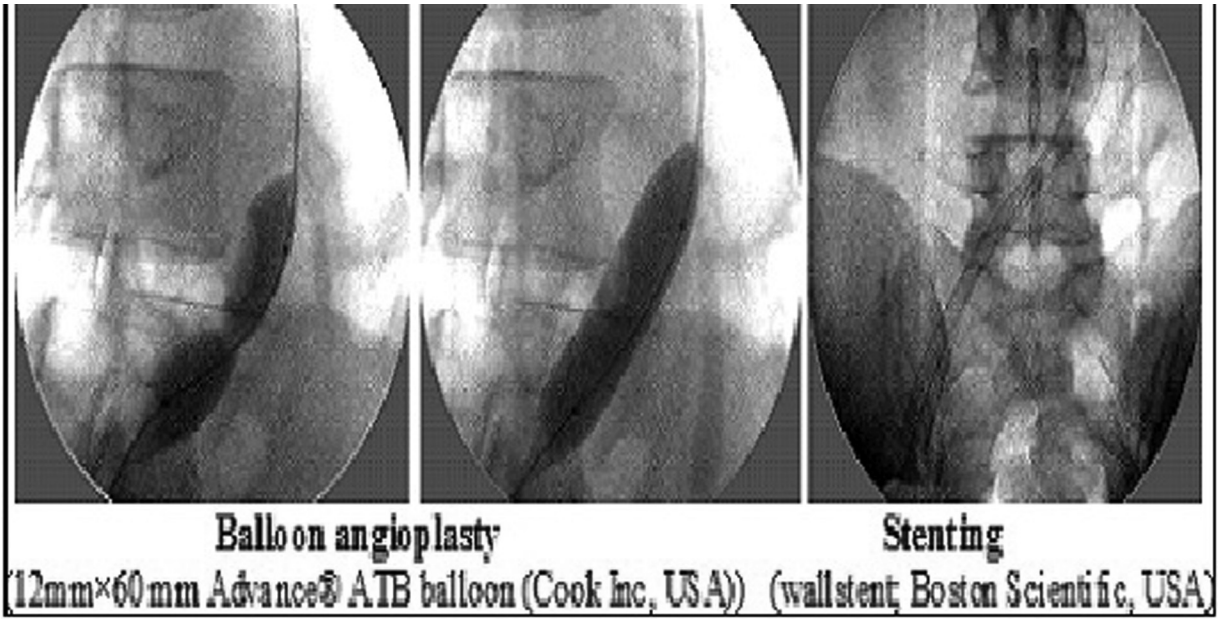
C-arm-guided wire insertion.

Figure 3



Left-sided femoropopliteal segment venography.

Figure 4



Proximal left common iliac vein.

Results

This prospective randomized controlled two-arm interventional study was conducted on 42 patients (47 limbs) with acute lower limb proximal DVT; 37 patients with unilateral limb and five patients with bilateral limbs. During the follow-up period of about 24 months, one patient of bilateral DVT died due to unrelated cause. So at completion of 24 months follow-up data, clinical status was available for 41/42 (97.6%) patients [45/47 limbs (95.7%)]; 20 patients (22 limbs) were assigned to CDT, group A and 21 patients (23 limbs) were assigned to the control group, group B. There was no statistical difference between both groups in demographic data (Table 1).

None of the patients in group A experienced allergic reactions nor contrast-induced nephropathy. CDT was performed at a median of 1 day after randomization. CDT patients passed uneventful course without procedure-related 1-month mortality.

Table 1 Patients' demographic and clinical data

Variables	Group A [20 (48.8)]	Group B [21 (51.2)]	Tests of significance	*P* value
Age (years)	42.6±3.8	44.2±4.5	Student '*t*'=1.71	0.09 (NS)
Sex				
Male	5 (25)	6 (28.6)	χ^2=0.017	0.89 (NS)
Female	15 (75)	15 (71.4)		
Duration of symptoms (days)	4.8±2.01	3.5±1.39	Z_{MWU}=1.09	0.27 (NS)
Treated limbs				
Left-sided	16 (80)	15 (71.4)	χ^2=2.88	0.23 (NS)
Right-sided	2 (10)	4 (19.1)		
Bilateral	2 (10)	2 (9.5)		

Data are presented as numbers (%) and mean±SD.

Culprit stenotic lesions in proximal common iliac vein were encountered in six patients. Four of these lesions were located on the left side and the other two were located on the right side. Balloon angioplasty was performed in all six patients (12, 14 ×60 mm, Advance ATB balloon; Cook Medical Inc., Chicago, USA). Stenting of the lesion was performed in five patients (two on the right side and three on the left side) with self-expanding wall stents (Wallstent Endoprothesis; Boston Scientific, USA). Left three stents varied from 14 to 16 mm diameter and their length varied from 70 mm (in three patients) to 90 mm (in the remaining 10 patients). But the right two stents were of 14 mm diameter and 60 mm length.

IVC filter insertion was not routinely used during CDT. Four (9.8%) cases were considered for filter insertion. This was because three patients developed PE; two patients in group A and one patient in group B and the last filter was used for fear of embolization from free-floating thrombus tail extending to the IVC. Celect filter was used (Cook Medical Inc.) in two patients and B/BRAUN Filter (Vena Tech LP; Vena Cava Filter System, France) in the other two patients. The choice of which filter was based on availability of the filter.

Two (10%) patients in the CDT group suffered pulmonary embolism in the form of sudden onset of retrosternal chest pain and dyspnea during passage of the wire through the thrombus. An IVC filter was immediately inserted through a right jugular venous puncture followed by initiation of catheter-directed thrombolytic drug instillation in the iliofemoral segment. The patients were then transferred to the ICU for oxygen mask and an urgent CT pulmonary angiography revealed the presence of subsegmental pulmonary embolism. Patient symptoms improved in the ICU and the second session of the procedure was accomplished as scheduled.

In group B, one (4.8%) patient had pulmonary embolism. This patient had hemoptysis at day 1 postrandomization. CT pulmonary angiography showed the presence of submassive PE. An IVC filter was immediately inserted through contralateral femoral venous puncture and this patient was transferred to the ICU, having no hemodynamic compromise. Anticoagulant therapy was continued with clinical improvement.

Daily monitoring of hemoglobin, INR, and platelet count did not reveal or indicate occult bleeding in any of the patients undergoing CDT or led to modification of the therapy. A total of three (15%) clinically relevant nonmajor bleeding complications were reported in the CDT group. There was one (5%) case of groin hematoma (contralateral, related to puncture of IVC filter placement), one (5%) case of popliteal fossa hematoma (related to the puncture sites), and last case (5%) of mild hematuria. All were managed conservatively. Micronized purified flavonoid fraction (MPFF, 450 mg diosmin plus 50 mg hesperidin-Daflon 500 mg; Servier, New Egypt, Cairo, Egypt) was prescribed and none had necessitated blood transfusion.

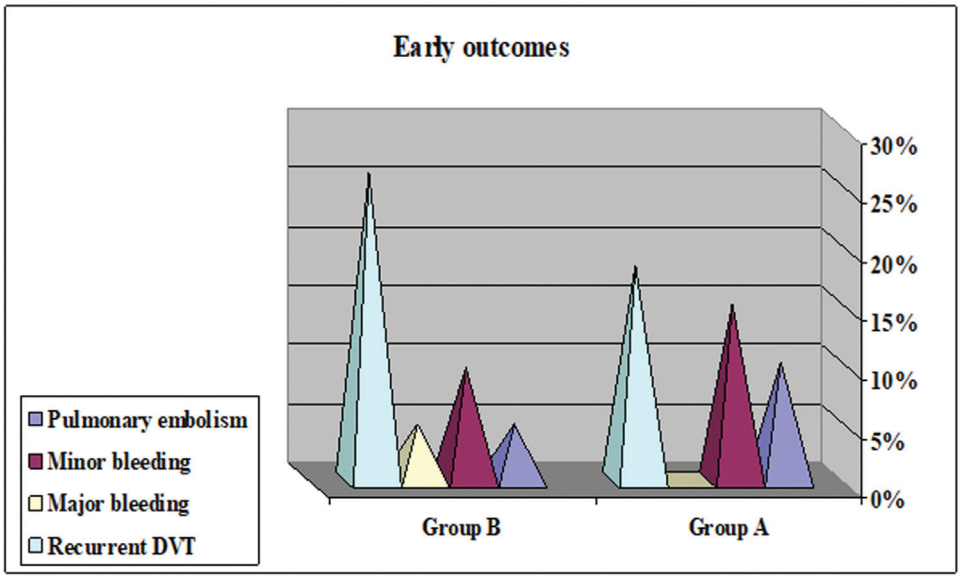
But in group B, three patients developed bleeding of which two(9.6%) had minor bleeding complications and the remaining one (4.8%) patient developed major bleeding. Patients with minor bleeding were managed conservatively; one of them had gynecological bleeding [menorrhagia without hemoglobin drop, they were prescribed (MPFF 450 mg diosmin plus 50 mg hesperidin-Daflon 500 mg, Servier)] and was advised to use it regularly during their menses and the other one developed gingival bleeding and epistaxis. Warfarin was resumed thereafter, with no further bleeding episodes during the follow-up period. The one (4.8%) patient who experienced major bleeding complications had massive subcutaneous trunk hematoma and intramuscular hematoma of right upper and lower limbs with a hemoglobin drop of 2 gm/dl in 3 days related to

Table 2 Postintervention early outcomes (*N*=45 limbs in 41 patients)

Variables	Group A [20 (48.8)]	Group B [21 (51.2)]	Tests of significance	*P* value
Pulmonary embolism	2 (10)	1 (4.8)	Z_{PROP}=0.82	0.41 (NS)
Bleeding				
Minor	3 (15)	2 (9.6)	χ^2=1.18	0.27 (NS)
Major	0	1 (4.8)		
Hospital stay (days)	3.2±1.45	5±2.03	Student '*t*'=3.03	0.003 (S)

Data are presented as numbers (%) and mean±SD.

Graph 1



Postintervention early outcomes.

anticoagulant therapy; the patient stopped warfarin; INR was normalized through transfusion of fresh blood and frozen plasma. Warfarin was temporarily withheld and substituted by LMWH for 1 week followed by reinstitution of warfarin. MPFF (450 mg diosmin plus 50 mg hesperidin-Daflon 500 mg; Servier) was prescribed also for 1 week. The mean duration of hospital stay was longer for group B (Table 2, Graph 1).

Given the concern of leg pain and swelling assessment during the first month, there was statistically significant difference between both groups; patients of group A complained of less pain at 10 and 30 days, *P* value 0.02 and 0.04, respectively. Also, there was significant decrease in leg circumference in group A at 10 and 30 days; *P* value 0.001 and 0.03, respectively (Table 3).

In group A, three patients (four limbs; 18.2%) had complete thrombolysis with insertion of a wallstent into a left common iliac vein stenotic lesion. They had recurrent symptoms at the follow-up visit. CT venography revealed occluded iliac vein stent. In group B, four patients (six limbs; 26.1%) had recurrent DVT. These patients were incompliant to anticoagulant therapy and were complaining of symptoms of recurrence (90 days postrandomization); their INR was 1.4–2.1. Duplex ultrasound showed recurrent iliofemoropopliteal DVT (Table 4, Graph 1).

At 6 months, there was statistically significant differences between both groups; patency of the iliac vein segment was better and femoral vein reflux was less in group A; *P* value less than 0.001 (HS) and 0.003 (S), respectively (Table 5).

At 1 year, patency of iliac vein segment was still high in group A, ($P<0.001$, HS). Also, other post-thrombotic changes were less in group A except residual thrombi in femoropopliteal vein ($P=0.87$, NS) (Table 6).

After 2 years, post-thrombotic changes were still significantly less in group A except iliac vein segment residual thrombi and wall thickening ($P=0.059$, NS and 0.17, NS, respectively), and residual thrombi in femoropopliteal vein lumen ($P=0.41$, NS) (Table 7, Figs 5 and 6).

Table 3 Leg pain and swelling assessment during the first month

Variables	Group A [20 (48.8)]	Group B [21 (51.2)]	*t*-test	*P* value
Change in leg pain severity				
First day	5.9±1.38	6.8±1.09	1.71	0.09 (NS)
10 days	4.26±1.28	5.53±0.99	2.14	0.02 (S)
30 days	3.71±1.27	4.99±0.98	3.41	0.04 (S)
Change in leg swelling (cm)				
First day	39.7±4.1	40.2±3.5	1.83	0.08 (NS)
10 days	39.41±3.93	40.48±3.34	4.16	0.001 (HS)
30 days	38.94±3.93	39.91±3.34	3.21	0.03 (S)

Data are presented as mean±SD and statistically significant difference by using unpaired *t*-test. HS, highly significant; S, significant.

Table 4 Incidence of recurrent deep vein thrombosis in the first[t] 6 months (*N*=45 limbs)

Recurrent DVT	Group A [20 (48.8)] [22 limbs (48.9%)]	Group B [21 (51.2%)] [23 limbs (51.1%)]	Z_{PROP}	*P* value
Unilateral DVT	2	2	0.032	0.97 (NS)
Bilateral DVT	1	2	0.55	0.58 (NS)
Total limbs	4 (18.2)	6 (26.1)	0.68	0.49 (NS)

Data are presented as numbers (%). DVT, deep vein thrombosis.

Table 5 Post-thrombotic changes at sixth month in both groups (*N*=45 limbs)

Variables	Group A [22 limbs (48.9%)]	Group B [23 limbs (51.1%)]	Z_{PROP}	*P* value
Iliac vein				
Patency	18 (81.8)	11 (47.8)	4.6	<0.001 (HS)
Residual thrombi	5 (22.7)	18 (78.3)	5.2	<0.001 (HS)
Wall thickening	6 (27.3)	17 (73.9)	4.85	<0.001 (HS)
Femoral vein				
Reflux	10 (45.6)	17 (73.9)	2.96	0.003 (S)
Residual thrombi	7 (31.8)	12 (52.2)	2.78	0.005 (S)
Sclerosis	8 (36.4)	15 (65.2)	2.96	0.003 (S)

Data are presented as numbers (%). HS, highly significant; S, significant.

Table 6 Post-thrombotic changes at 1 year in both groups (*N*=45 limbs)

Variables	Group A [22 limbs (48.9%)]	Group B [23 limbs (51.1%)]	Z_{PROP}	*P* value
Iliac vein				
Patency	18 (81.8)	12 (52.2)	4.34	<0.001 (HS)
Residual thrombi	4 (18.2)	9 (39.1)	2.46	0.014 (S)
Wall thickening	5 (22.7)	13 (56.5)	2.81	0.0049 (S)
Femoral vein				
Reflux	12 (54.6)	19 (82.6)	3.08	0.002 (S)
Residual thrombi	4 (18.2)	6 (26.1)	0.17	0.87 (NS)
Sclerosis	7 (31.8)	15 (65.2)	3.16	0.0016 (S)

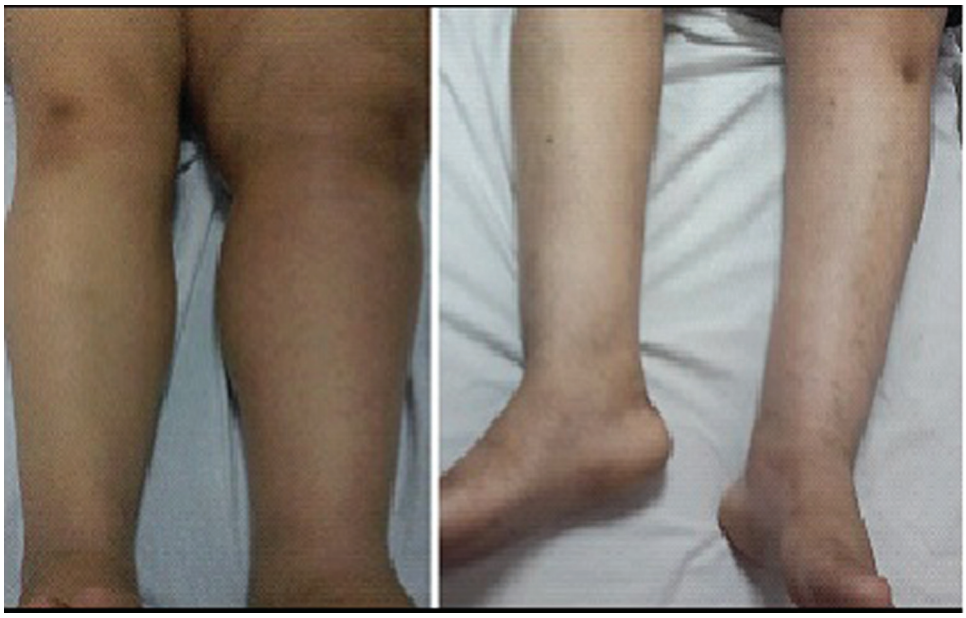
Data are presented as numbers (%). HS, highly significant; S, significant.

Table 7 Post-thrombotic changes at 2 years in both groups (*N*=45 limbs)

Variables	Group A [22 limbs (48.9%)]	Group B [23 limbs (51.1%)]	Z_{PROP}	*P* value
Iliac vein				
Patency	18 (81.8)	13 (56.5)	4.12	<0.001(HS)
Residual thrombi	2 (9.1)	6 (26.1)	1.88	0.059 (NS)
Wall thickening	7 (31.8)	11 (47.8)	1.34	0.17 (NS)
Femoral vein				
Reflux	17 (77.3)	21 (91.3)	3.27	<0.001 (HS)
Residual thrombi	2 (9.1)	4 (17.4)	0.81	0.41 (NS)
Sclerosis	8 (36.7)	18 (78.3)	3.6	<0.001 (HS)

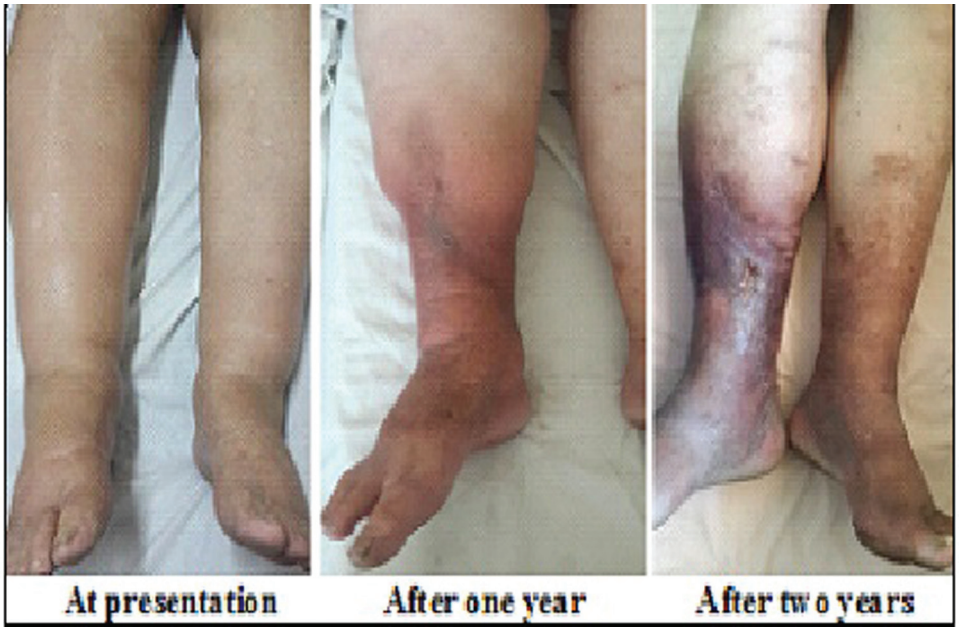
Data are presented as numbers (%). HS, highly significant; S, significant.

Figure 5



Left iliofemoral deep vein thrombosis (left photo) which resolved after catheter-directed thrombolysis (right photo).

Figure 6



Right iliofemoral deep vein thrombosis allocated conventional therapy with severe post-thrombotic syndrome.

By reviewing the incidence and severity of PTS using the Villalta score, patients in group A developed significantly less PTS at 6 months, 1 year, and 2 years (P=0.024, 0.017, and 0.035, respectively). Moreover, severe cases were significantly less in group A; at 6 months and at 2 years (P=0.035 and 0.042, respectively) (Table 8, Graph 2).

PTS severely impacts the quality of life of affected individuals; in this study, patients of group A experienced significantly better quality of life (P=0.003) (Table 9).

Discussion

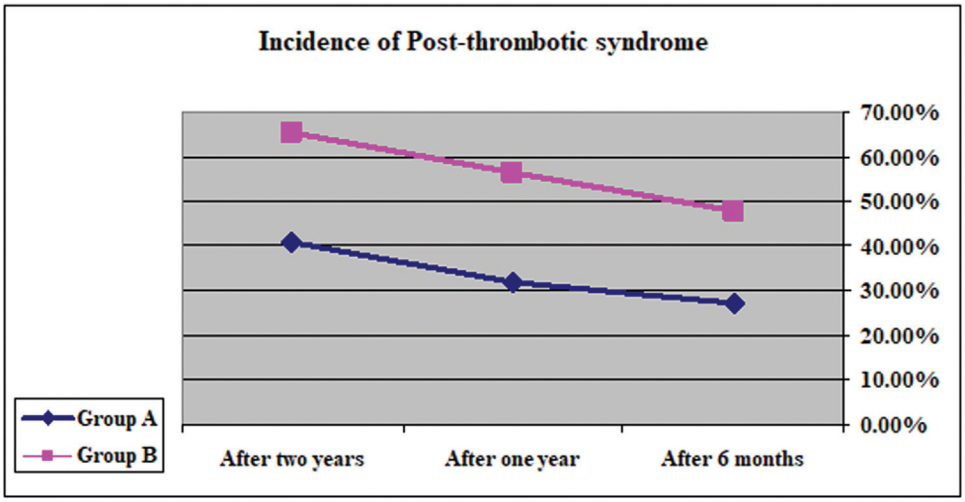
Early removal of thrombus may improve deep venous flow and reduce valvular reflux and incidence of PTS. Early thrombus removal can be achieved by surgical thrombectomy, systemic thrombolysis, CDT, and/or pharmacomechanical thrombolysis [15–17].

Table 8 Severity grading of post-thrombotic syndrome using the Villalta score in both groups (*N*=45 limbs)

Post-thrombotic syndrome	Group A [22 limbs (48.9%)]	Group B [23 limbs (51.1%)]	Z_{PROP}	*P* value
After 6 months	6 (27.3)	11 (47.8)	2.24	0.024 (S)
Villalta severity category				
Mild	3 (50)	2 (18.2)	2.22	0.026 (S)
Moderate	3 (50)	2 (18.2)	2.22	0.026 (S)
Severe	0	7 (63.6)	2.1	0.035 (S)
After 1year	7 (31.8)	13 (56.5)	2.38	0.017 (S)
Villalta severity category				
Mild	3 (42.9)	4 (30.8)	1.76	0.078 (NS)
Moderate	3 (42.9)	6 (46.2)	2.16	0.031 (S)
Severe	1 (14.2)	3 (23.1)	0.72	0.47 (NS)
After 2 years	9 (40.9)	15 (65.2)	2.1	0.035 (S)
Villalta severity category				
Mild	6 (66.7)	5 (33.3)	0.81	0.57 (NS)
Moderate	2 (22.2)	6 (40)	2.15	0.031 (S)
Severe	1 (11.1)	4 (26.7)	1.93	0.042 (S)

Villalta severity category; mild (score 5–9), moderate (score 10–14) or severe (score >14). Data are presented as numbers (%). HS, highly significant; PTS, post-thrombotic syndrome; S, significant.

Graph 2



Incidence of post-thrombotic syndrome.

Table 9 Quality of life (symptoms) during the 24-month follow-up

Variables	Group A [20 (48.8)]	Group B [21 (51.2)]	*t*-test	*P* value
Change in VEINES-QOL	25±2.03	23.2±1.45	3.03	0.003 (S)

Data are presented as numbers (%) and mean±SD and statistically significant difference by using the unpaired *t*-test. VEINES-QOL, Venous Insufficiency Epidemiological and Economic Study Quality of Life.

In this study, 73.1% of patients were women. This was near similar to studies done by Elsharawy and Elzayat [13], Bækgaard *et al.* [18], Protack *et al.* [19], and Manninen *et al.* [20]: 68.57, 77.22, 61, and 54% of patients were women, respectively. On the contrary, only 37 and 49.06% of patients enrolled in the CaVenT and the Lee *et al.* trial were women, respectively [21,22].

Left-sided DVT was reported in this study in 31 (75.6%) patients, which was less than that mentioned in the study of Sillesen *et al.* [23] (84.44% of patients) and was more than that reported in the CaVenT trial (58.52% of patients) [24].

Access to venous system was gained through sonographic-guided ipsilateral popliteal vein in prone position. This was similar to access done by Beakgaard *et al.* [18] stipulated presence of patent distal half of popliteal vein is necessary to act as an access.

By reviewing the success of thrombolysis, it was noticed that complete lysis was achieved in 17 (85%) patients. These results were comparable to that mentioned by Gomaa *et al.* [25] who reported that complete lysis was achieved in 23/28 (82.2%) patients and partial lysis was achieved in 4/28 (14.3%). Also, the results were comparable with studies done by Elsharawy and Elzayat [13], Enden *et al.* [21], Sillesen *et al.* [23], and Chang *et al.* [26] who mentioned complete lysis that was achieved in 61, 88.89, 93, and 80%, respectively.

Alteplase was used in this study because streptokinase had been abandoned due to its allergic complications [27]. Our results were significantly better than the result of Mewissen *et al.* [28] who achieved complete lysis rate in only 31% using urokinase. This discrepancy is due to the higher fibrin specificity of Alteplase than urokinase.

The mean duration of symptoms was 4.8±2.01 days (1–14 days); meta-analysis was performed by Casey *et al.* [29], who stated that there was no significant effect of duration between the onset of symptoms and the time of delivering intervention within the 14-day therapeutic window. The timing of CDT has been a matter of debate; the clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum accepted 14 days as the cutoff for CDT in DVT treatment [17]. Also, ATTRACT and CaVenT trials used cutoff limits of 14 and 21 days from the start of symptoms, respectively [30]. On the other hand, Dumantepe *et al.* [31] by using ultrasound-accelerated thrombolysis reported successful results in DVT patients of more than 90 days. Of their 12 patients, six had complete lysis while five had partial lysis with an average duration of 26 h.

Among patients of group A, culprit stenotic lesions in the proximal common iliac vein were encountered in six patients. Balloon angioplasty was performed in all, but stenting was performed in 5/6 (83.33%) patients. These results were comparable to the study done by Sillesen and colleagues 30/45 occluded veins (67%) revealed underlying stenoses in iliac veins. All were treated with balloon angioplasty and stenting [23]. In CaVenT trial, 23/90 (25.56%) patients received balloon angioplasty and 15/23 (65.2%) patients received venous stents [26].

CDT has two drawbacks: it is invasive with bleeding risk. During the current study, a total of 3 (15%) patients with clinically relevant nonmajor bleeding complications were reported in the CDT group which is less than that found by Gomaa and colleagues; there was only ecchymosis at the puncture site in 10/28 patients (35%) [29], Sillesen *et al.*; 16% [23] and Verhaegue *et al.*; 12 patients (50%) had bleeding at the puncture site with six patients needing blood transfusion. This was mostly due to use of a low to medium dose of alteplase (1 mg/h) in comparison to Verhaege *et al.* [32], who used a high dose of 3 mg/h. But this bleeding complications were similar to that reported by CaVenT trial, 9% at the puncture site [21].

By reviewing the incidence of pulmonary embolism two (10%) patients in the CDT group and one (4.8%) patient in group B had pulmonary embolism. Nevertheless, PE had no effect on conductance and subsequent follow-up. Enden *et al.* [33], in early results of CaVenT trial, observed no pulmonary embolism due to CDT.

In group A, three patients (four limbs; 18.2%) versus four patients (six limbs; 26.1%) in group B had recurrent DVT; this result was similar to the reports of CaVenT trial; 34 (19%) patients had recurrent DVT with no difference between the treated groups [24]. On the basis of findings of the current study and findings of CaVenT trial, it can be assumed that addition of CDT to standard anticoagulant therapy does not have additional protection against recurrent DVT.

Given the concern of leg pain and swelling assessment during the first month, there was statistically significant difference between both groups. This result was near similar to that approved by ATTRACT trial investigators who reported that there was change in leg pain severity, baseline to day 10 and day 30; *P* value: 0.02 and 0.03, respectively, and change in leg circumference, baseline to day 10 and day 30; *P* value 0.02 and 0.05, respectively [34].

As regards post-thrombotic morbidity, after 6 months, patency of iliac vein segment was significantly better and femoral vein reflux was significantly less in group A. These results were comparable to that mentioned by CaVenT trial; after 6 months follow-up, patency of iliofemoral vein segment was found in 64% of patients in the CDT group and 35.8% of patients in the control group while femoral venous insufficiency and other post-thrombotic changes did not differ significantly in treated arms [33]. At 1 year, patency of iliac vein segment was still high and other post-thrombotic changes were less in group A as mentioned by

Mewissen *et al*. [28] who reported that vein patency might be twice as good after total clot removal.

It is assumed that both recanalization and development of reflux are continuing processes, mainly established during the first 2 years following DVT. At 2 years of the current study, post-thrombotic changes were still less in group A as mentioned in the CaVenT trial; deep vein reflux reduced after 2 years and iliofemoral patency improved after 6 months to 2 years [13]. Also, this result was comparable to studies done by AbuRahma *et al*. [35]; 2 years follow-up period symptom resolution was 78% in the CDT group versus 30% in the group treated with anticoagulation and Ly *et al*. [36]; reflux was found in 32% after 24 months.A limitation in clinical studies on PTS is the absence of a gold standard for its diagnosis. Several scoring systems have been used for diagnosis and severity grading of chronic venous disorders. In the current study, Villalta score had been used to diagnose and to grade PTS. After a follow-up period of 24 months, patients in group A developed less PTS at 6 months, at 1 year, and at 2 years; *P* value: 0.024, 0.017, and 0.035, respectively; this result was near similar to CaVenT trial. After a 2-year follow-up period, 43% of patients in CDT developed PTS compared with 71% in the control group [25]. Our results regarding PTS were against ATTRACT trial, which might be due to our early intervention in most cases in the first few days of DVT onset and our patients were younger and some patients of the ATTRACT trial had DVT in the femoropopliteal segment only [34].

In a Cochrane review, Watson *et al*. [37] performed a meta-analysis of 17 RCT totaling 1103 patients. They found that thrombolysis offers potential advantages over standard treatment, by reducing the proportion of patients with PTS by a third in the longer term, particularly in patients with iliofemoral vein thromboses.

Given the special concern of PTS that severely impacts the quality of life of affected individuals by lost productivity, loss of functional independence and forced retirement, in the current study patients of group A experienced better quality of life due to less PTS patients (P=0.003). This was reported by Kahn *et al*. [5] in a multicenter cohort study that recruited 357 patients with acute DVT. PTS was the principal determinant of health-related quality of life at 2 years of follow-up. But ATTRACT trial investigators reported that change in VEINES disease-specific quality of life, symptoms, and changes from baseline to 2 years were insignificant in both groups (P=0.17) [34].

Conclusion

Addition of CDT in the treatment of acute iliofemoral DVT was safe and tolerated by most of the patients with better effect to reduce leg pain and circumference. It was considered a protecting weapon to prevent PTS and to improve quality of life and was related to achievement of higher iliac vein patency and less reflux.

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Conflicts of interest

There are no conflicts of interest.

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