Clinical and radiological outcomes of adjuvant catheter-directed thrombolysis of acute iliofemoral venous thrombosis compared to standard anticoagulant therapy: a randomized controlled study

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Background
For many years, in the open vein hypothesis, it has been assumed that rapid thrombus elimination and restoration of unobstructed deep venous flow may prevent valvular reflux, venous obstruction, and postthrombotic syndrome (PTS); however, there is a controversy between trials about the validity of this hypothesis.
Objectives
To assess the benefit of adjuvant catheter-directed thrombolysis (CDT) in the prevention of PTS compared with standard therapy in patients with first-time iliofemoral deep-vein thrombosis.
Patients and methods
From January 2018 to October 2021, patients aged 18–70 years with a first-time iliofemoral deep venous thrombosis were recruited for this randomized controlled trial. Eligible patients with symptoms for no more than 21 days were randomly assigned to either adjuvant CDT with standard anticoagulation or standard anticoagulant treatment alone. PTS incidence as assessed by Villalta score at 12 months was the primary outcome of this study. Our secondary objectives were to describe the frequency of chronic postthrombotic changes, residual vein thrombosis, deep venous reflux, and deep venous thrombosis recurrence rates within 12 months of follow-up.
Results
At the completion of 12 months of follow-up, data were available for 92 patients (47 in the CDT group, 45 in the control group). Baseline characteristics and risk factors were comparable between the two groups. CDT was associated with a significant reduction of PTS incidence [10.6% in the CDT group and 31.1% in the control group; risk ratio (RR), 0.34; 95% confidence interval (CI), 0.13–0.87; P=0.024]. Duplex ultrasound findings revealed statistically significant lower residual vein thrombosis in the CDT group [12.7% compared with 37.8% in the control group (RR 0.42; 95% CI, 0.22–0.77; P=0.005); chronic postthrombotic vein changes were detected in 12.76% in CDT group versus 37.8% control group (RR 0.34; 95% CI, 0.14–0.78; P=0.01]; deep venous reflux was significantly lower in CDT compared with standard treatment patients (8.5 vs. 24.4%; RR 0.31; 95% CI, 0.12–0.89; P=0.03); thrombosis recurrence was comparable in the two treatment groups (4.25 vs. 11.1%) with no significant statistical difference (P=0.023). Subgroups analysis revealed significantly increased risk of PTS among patients of residual vein thrombosis (RR 0.31; 95% CI, 0.11–0.89; P=0.028), patients with chronic postthrombotic vein changes (RR 2.7; 95% CI, 1.25–5.8; P=0.01), and deep venous reflux (RR 2.37; 95% CI, 1.07–5.24; P=0.03). On the other hand, no significant correlation was detected between thrombosis recurrence and PTS (RR 1.42; 95% CI, 0.41–4.96; P=0.57). Subgroups analysis also revealed increased risk of thrombosis recurrence among patients with residual vein thrombosis (RR 10.72; 95% CI, 1.35–85.33; P=0.02).
Conclusion
The addition of CDT to anticoagulation resulted in a lower risk of PTS. CDT led to reduced late residual thrombus burden, chronic postthrombotic vein changes, and deep venous reflux. Duplex ultrasound changes including deep venous reflux, residual vein thrombosis, and chronic postthrombotic vein changes can be considered predictors for PTS.

Keywords:
catheter-directed thrombolysis, deep venous thrombosis, postthrombotic syndrome

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Introduction

Venous thromboembolism (VTE) represents a major worldwide health concern, estimated to affect one to two persons per 1000 people in the USA each year.

Deep venous thrombosis (DVT) represents about two-thirds of VTE cases, while pulmonary embolism (PE) is responsible for almost all VTE-related deaths [1,2]. The risk of PE following DVT is well established, but the late vascular sequelae of DVT are often underappreciated, costly to manage, and can adversely affect the quality of life [3].

In an acute attack of DVT, inflammatory damage of venous valves develops, and that results in persistent venous obstruction and/or reflux that lead to chronic venous hypertension which is the main cause of postthrombotic syndrome (PTS) [4]. The main goals of DVT treatment are restoring venous patency, preventing thrombus extension, and reducing the incidence of PE. Long-term therapeutic goals include minimizing the incidence of recurrent thrombosis and decreasing the risk of chronic venous insufficiency and PTS [5].

The current standard treatment of DVT is systemic anticoagulant therapy. Effective anticoagulant therapy targets at prevention of thrombus propagation, decreasing recurrent attacks either early or late, and minimizing the incidence of PE [6]. However, anticoagulant therapy has no role in the lysis of the thrombus and recanalization of the vein; it depends on the endogenous fibrinolytic activity. If lysis of the thrombus is complete, early recanalization occurs, venous patency is regained earlier and valve function may be preserved, and vice versa [7]. Incomplete recanalization with residual vein thrombosis significantly increases the risk of DVT recurrence [8].

Consequently, larger-volume clots, particularly iliofemoral DVTs, are a therapeutic challenge, as anticoagulation often fails to restore venous patency and thus predisposes the patient to recurrent thrombosis and chronic complications due to associated venous valvular disruption [9]. These limitations provoked the development of thrombus removal and dissolution strategies, including catheter-directed thrombolysis (CDT), pharmacomechanical CDT, and percutaneous mechanical thrombectomy. The indications for and effectiveness of these techniques remain subjects of investigation; however, there is increasing evidence supporting the use of these modalities for the treatment of patients with iliofemoral DVT in appropriately selected cases [10].

Patients and methods

Study objectives

The primary objective of this study is to investigate the efficacy of adjunctive CDT in the reduction of incidence of PTS at 12 months follow-up in patients with first-time acute iliofemoral DVT. Our secondary objectives are to describe the frequency of chronic postthrombotic changes, residual vein thrombosis, deep venous reflux, and DVT recurrence rates at duplex ultrasound examination within 12 months follow-up.

Study design and participants

This study was designed as a randomized controlled trial at the Department of Vascular Surgery, Menoufia University Hospitals. From January 2018 to October 2021, and after approval of our institutional ethical committee, 100 patients with acute iliofemoral DVT were recruited. After written informed consent, eligible patients were randomized using a computerized list into two groups; the first group (CDT group) was treated by CDT followed by conventional anticoagulant therapy. The second group (control group) was treated with conventional anticoagulant therapy only.

Patient selection

Adult patients with first-time acute iliofemoral DVT confirmed by duplex ultrasound and with symptom duration of up to 21 days were eligible for inclusion. Complete inclusion and exclusion criteria are presented in Table 1.

Procedures

Patients allocated in control group started treatment immediately by low molecular weight heparin (LMWH) (enoxaparin) for 10 days, oral warfarin started in day 2 and continued for at least six months with target international normalized ratio (INR) of 2.0–3.0.

For patients allocated in the CDT group, LMWH was discontinued for at least 12 h, and oral anticoagulant therapy was discontinued to obtain an INR less than 1.5. CDT is started on the first following work day, at the start procedure, 5000 U of unfractionated heparin (UFH) was given intravenously followed by a continuous intravenous infusion of UFH at rate of 15–20 U/kg/h) with adjustment of activated partial thromboplastin time at 1.5–2 times normal, that is, at 40–60 s, during CDT.

All procedures were performed in the operating room under complete aseptic conditions. After applying a local anesthetic agent, guided by ultrasound, a 6 Fr introducer sheath was inserted into the ipsilateral popliteal vein. Venography was performed first from the sheath using nonionic contrast dye to determine the

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Age 18–70 years
First-time acute iliofemoral DVT
Symptom duration up to 21 days
Exclusion criteria
Contraindications to thrombolysis or anticoagulant treatment
Patients indicated for thrombolytic treatment, for example, phlegmasia caerulea dolens or isolated vena cava thrombosis
Severe anemia (hemoglobin <8 g/dl)
Thrombocytopenia (platelets <150 000/μl)
Renal impairment
Uncontrolled hypertension (persistent systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg)
Pregnancy or DVT within 21 days postpartum
Recent surgery or trauma (≤14 days)
History of subarachnoid or intracerebral bleeding
Life expectancy less than 24 months
Mental disease that may interfere with treatment and follow-up
Former ipsilateral deep-vein thrombosis
Patients receiving chemotherapy

DVT, deep venous thrombosis.

site and extension of the thrombus through the vein. Then, the guide wire and catheter were advanced above the proximal extent of the thrombus followed by adequate-size perfusion catheters (fountain catheter; 30–50 cm). Twenty milligrams of alteplase (actilyse) diluted in 500 ml of normal saline (NaCl 0.9%) was infused at 0.01 mg/kg/h for a maximum of 96 h with maximal dose of 20 mg/24 h.

Treatment continued in a medical ward. Blood pressure and pulse were recorded and the puncture site was monitored for bleeding. Daily analysis of hemoglobin, INR, and platelet counts were recorded. Activated partial thromboplastin time is monitored twice daily for adjustment of heparin dose.

Venography was done daily by injecting the contrast dye through the perfusion catheter to evaluate the efficacy of thrombolytic therapy catheters was repositioned accordingly, and thrombolysis is graded by a scoring system. Each venous segment was given a score, where 0=patent vein, 1=partially occluded vein, and 2=completely occluded vein. The total thrombus scores before and after thrombolysis were calculated by adding the segmental scores. Thrombolysis grade can be estimated by calculating the difference between the prethrombus and postthrombus scores divided by the prelysis score. Grade I less than equal to 50%; grade II (51–90%) partial lysis (lysis of part of the thrombus), and grade III (100%) (complete lysis of all detachable thrombus in the venous segment)=patent lumen [11].

Antithrombotic agents other than UFH were discontinued during the thrombolysis procedure. Bleeding was classified major if led to a drop of 2 g/dl hemoglobin, or in a critical organs such as the brain and retroperitoneal region, while clinically relevant nonmajor bleeding included epistaxis, a visible large puncture site hematoma, or gross hematuria [12].

The procedure was terminated after 96 h of treatment or if complete lysis was detected. The infusion catheter was removed immediately after the end of the procedure, and hemostasis is obtained by manual compression of the puncture site and continued for 2 h using a bandage with tight wrapping while the patient is immobilized. LMWH was initiated 1 h after the end of the procedure and continued with oral anticoagulation as described earlier for 6 months. All patients in both groups were advised to use knee-high compression stockings, class II, daily for 12 months.

Follow-up

Patients of both groups were evaluated clinically at the outpatient clinics every 2 weeks and the warfarin dose was adjusted to maintain the INR level within the therapeutic range. Duplex ultrasound examination of the lower limb veins was performed after 3, 6, 9, and 12 months of initiation of treatment by one radiologist blinded by the patient's previous treatment regimen and medical history. The compressibility of the femoral vein was evaluated using Gray-scale ultrasound while iliofemoral venous flow and insufficiency (reflux) were evaluated using Doppler ultrasound. Venous insufficiency was evaluated in the standing position. Reflux of the deep venous system was defined as a reversal of the velocity curve lasting longer than 1 s after standardized distal pneumatic decompression [13]. Other radiological findings including residual vein thrombosis, chronic postthrombotic changes, and

thrombosis recurrence were recorded. Residual vein thrombosis was considered present if there was noncompressibility of more than 40% of the vein diameter [14]. Chronic postthrombotic changes refer to persistent partial or complete venous obstruction with Fibrosis producing vein scarring, wall thickening, and synechiae [15]. Recurrent DVT was defined as thrombosis of a venous site that was either previously uninvolved or had interval documentation of incident thrombus resolution [16]. PTS was diagnosed with the Villalta scale and patients were classified with PTS if the score was 5 or more, or if a venous ulcer was present (Table 2) [17].

Statistical analysis

On basis of a review of the literature, we assumed that the prevalence of PTS would be about 35% (20–50%) in patients allocated in anticoagulant therapy treatment as compared with about 10% in those allocated in the CDT group. At a significance level of 5% and a statistical power of 80%, 43 patients had to be included in each study group. Statistical analysis was by intention to treat [18].

Statistical analysis was performed using SPSS, version 24.0. (IBM Corp., Armonk, New York, USA). Qualitative data were described using numbers and percentages. Quantitative data were described using mean and SD for parametric data after testing normality using Kolmogrov–Smirnov test. *P* value of less than 0.05 was considered statistically significant.

For data analysis, the χ^2 test for comparison of two or more groups, Fisher's exact test was used as a correction for χ^2 test when more than 25% of cells have a count of less than 5 in 2 × 2 tables. For quantitative data between groups, Student's *t* test was used to compare two independent groups, Paired *t* test was used to compare two periods in the same group.

Results

From January 2018 to October 2021, out of 3179 DVT patients, 100 patients fulfilling our inclusion criteria were enrolled and randomly assigned into two groups each containing 50 patients. No significant differences were seen between both groups regarding baseline characteristics and risk factors (Table 3).

CDT, catheter-directed thrombolysis; COVID-19, coronavirus disease 2019; DVT, deep venous thrombosis; PE, pulmonary embolism.

Study profile of the 100 patients recruited and randomized between January 2018 and October 2021 was illustrated in Fig. 1. In CDT group, procedure was aborted in two cases; one due to failure to introduce the guide wire and catheter due to venous anomaly, the other patient developed gross hematuria few hours after initiation of treatment. Forty seven patients completed follow-up period, one patient withdrew before the start of treatment, and another two patients were lost during follow-up period. From the 50 patients enrolled in the anticoagulant group, only 45 patients completed the treatment course and during the 12 months follow-up period, four patients withdrew from the study and one patient died from another cause, not related to anticoagulant therapy.

In the CDT group, as illustrated (Fig. 2), complete lysis (grade III) was achieved in 18 patients, while,

Table 2 Villalta scale for assessment of postthrombotic syndrome [17]

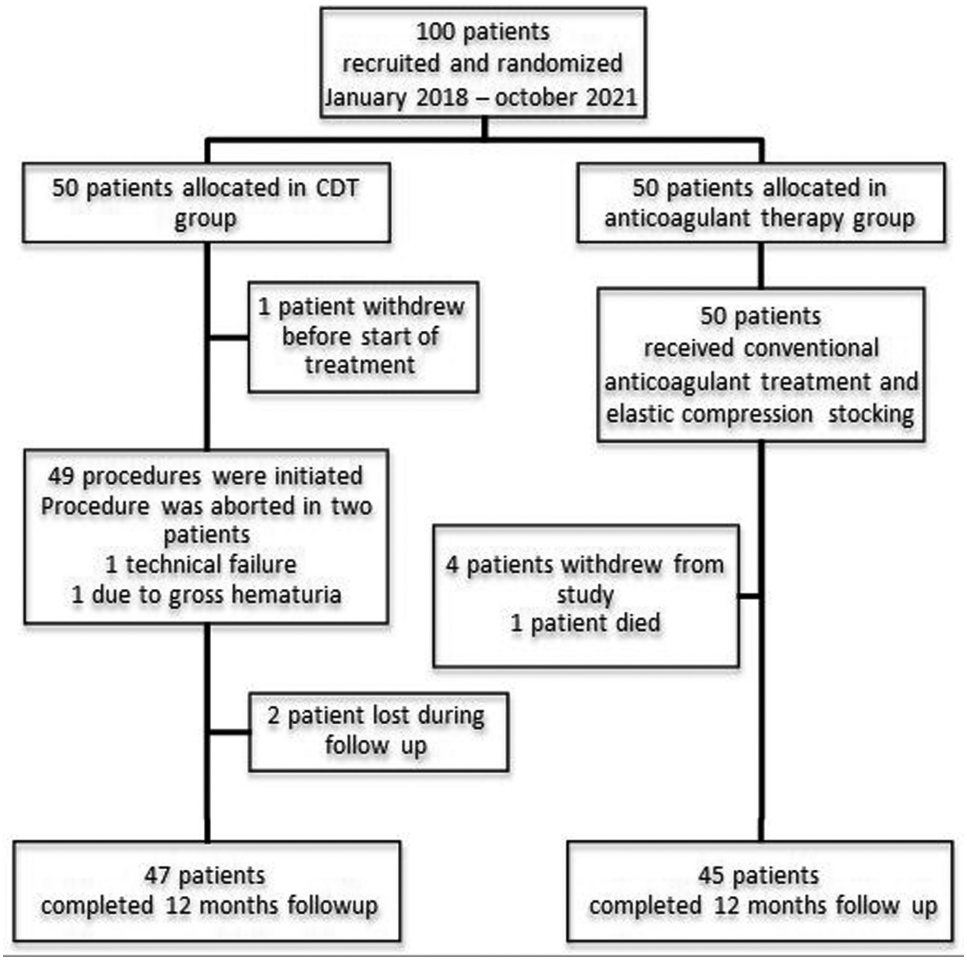
	None	Mild	Moderate	Severe
Patient-rated venous symptoms				
Pain	0	1	2	3
Cramps	0	1	2	3
Heaviness	0	1	2	3
Paresthesia	0	1	2	3
Pruritus	0	1	2	3
Clinician-rated signs				
Pretibial edema	0	1	2	3
Skin induration	0	1	2	3
Hyperpigmentation	0	1	2	3
Pain during calf compression	0	1	2	3
Venous ectasia	0	1	2	3
Redness	0	1	2	3
Venous ulcer				Present
		Scoring		

Each sign or symptom is rated as 0 (none), 1 (mild), 2 (moderate), or 3 (severe), and summed to produce a total score.
A total score of <5 indicates no PTS, mild (5–9), moderate (10–14), to severe (≥15 or venous ulceration).

Table 3 Baseline characteristics and risk factors of both groups

	CDT group (*N*=47) [*n* (%)]	Control group (*N*=45) [*n* (%)]	*P* value
Age (mean±SD)	41.9±6.2 years	43.4±5.7 years	0.23
Sex (female/male)	31/16	24/21	0.28
Duration of symptoms (mean±SD)	6.9±4.3 days	5.7±3.6 days	0.15
Extent of the thrombus [*n* (%)]			
Iliofemoral	14 (29)	18 (40)	0.4
Femoral	33 (71)	27 (60)	
Recent surgery (14–60 days)	4 (8)	7 (15)	0.35
History of trauma	3 (6.4)	0	0.24
Oral contraceptive pills or hormone replacement therapy	11 (23)	5 (11)	0.17
History of infections in last 6 weeks including COVID-19	2 (4)	7 (14)	0.10
Thrombophilia	7(14)	11(22)	0.3
Previous contralateral DVT or PE	4 (8)	9 (18)	0.14

Figure 1



Study patients' profile.

grade II lysis (50–90% lysis) was achieved in 27 patients. Among the four CDT patients with grade I lysis, two procedures were prematurely ended; one developed gross hematuria a few hours after initiation of treatment, and the other procedure was terminated due to technical failure. The mean duration of CDT procedures was 2.8 (±0.71) days.

The mean duration between the start of symptoms and initiation of CDT ranged from 2 to 17 days with a

mean duration of 7.2±3.75 days. The mean duration of hospital stay was 8.1±1.24 days in the control group versus 7.8±1.05 days in the CDT group (*P* value 0.19).

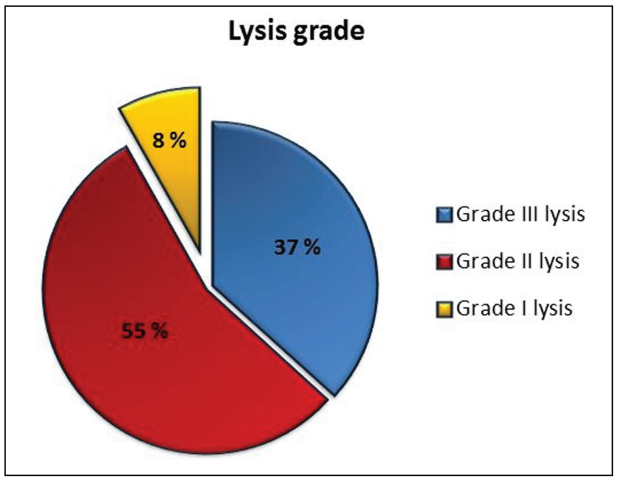
Two patients in the control group had a symptomatic PEs (4%) that were admitted to ICU and treated conservatively, one patient developed massive hematemesis and was referred to endoscopy after cessation of treatment.

In the CDT group, three patients had high fever (6%), four patients had puncture site hematoma that was managed conservatively by compression (8%), and one patient developed gross hematuria early during the procedure. Daily analysis of hemoglobin, during the CDT procedure, did not reveal or indicate occult bleeding in the other patients or led to the modification of the therapy. There were no pulmonary embolization or deaths related to CDT. In one case of DVT that was caused by May–Thurner syndrome and after near total thrombus dissolution with thrombolysis, the residual left common iliac vein stenosis was treated by means of angioplasty and stenting. No statistical significance was detected between the two groups regarding the incidence of major, nonmajor bleeding, or pulmonary embolization.

The cumulative incidence of PTS at 12 months, according to Villalta score, was five (10.6%) out of 47 patients received adjuvant CDT compared with 14 (31.1%) out of 45 patients who received standard treatment only with a statistically significant superiority of CDT in preventing PTS (RR 0.341; 95% CI, 0.134–0.871; *P*=0.024). the analysis of the severity of PTS in both groups revealed only a statistical difference in the incidence of moderate PTS while no significant difference detected in mild or severe PTS, in CDT patients mild PTS was detected in five (10.6%) cases versus eight (17.8%) cases in the control group (RR 1.2972; 95% CI, 1.041–1.616; *P*=0.33); no moderate PTS detected in CDT patients while six (13.3%) cases were recorded in standard treatment patients (*P*=0.02); no severe PTS or chronic venous ulcers were detected in both groups. (Table 4)

Analysis of duplex ultrasound finding in both groups revealed statistically significant lower residual vein thrombosis in the CDT group (12.7%) compared with the control group (37.8%) (RR 0.416; 95% CI, 0.22–0.77; *P*= 0.005); chronic postthrombotic vein changes were detected in six out of 47 (12.76%) cases in CDT group versus 17 out of 45 (37.8%) patients in the control group (RR 0.337; 95% CI, 0.14–0.78; *P*=0.01); deep venous reflux was significantly lower in CDT compared with standard treatment patients (8.5 vs. 24.4%) (RR 0.309; 95% CI, 0.1068–0.896; *P*=0.03); incidence of thrombosis recurrence was comparable in the two treatment groups (4.25 vs. 11.1%) with no significant statistical difference (*P*=0.023) (Table 4).

Figure 2



Results after CDT procedures. CDT, catheter-directed thrombolysis.

Table 4 Postthrombotic syndrome and duplex ultrasound findings in both groups

	CDT group (*N*=47) [*n* (%)]	Control group (*N*=45) [*n* (%)]	Risk ratio (95% CI)	*P* value
Postthrombotic syndrome at 12 months	5 (10.6)	14 (31.1)	0.34 (0.13–0.87)	0.024
None (<5)	42 (89.4)	31 (68.9)	1.29 (1.04–1.62)	0.02
Mild (5–9)	5 (10.6)	8 (17.8)	0.59 (0.21–1.69)	0.33
Moderate (10–14)	0	6 (13.3)	0.074 (0.004–1.27)	0.02
Severe (≥15)	0	0	0.96 (0.019–47.3)	0.98
Venous ulcer	0	0	0.96 (0.019–47.3)	0.98
Duplex ultrasound findings in both groups				
Residual vein thrombosis (6 months)	10 (21.3)	23 (51.1)	0.42 (0.22–0.77)	0.005
Chronic postthrombotic changes (12 months)	6 (12.8)	17 (37.8)	0.34 (0.15–0.78)	0.01
Deep venous reflux	4 (8.5)	11 (24.4)	0.31 (0.10–0.89)	0.03
DVT recurrence	2(4.25)	5 (11.1)	0.38 (0.078–1.87)	0.23

CDT, catheter-directed thrombolysis; CI confidence interval, DVT, deep venous thrombosis.

Assessment of correlation between duplex ultrasound findings and PTS revealed significantly increased risk of PTS among patients of residual vein thrombosis (RR 0.309; 95% CI, 0.1068–0.896; *P*=0.028); PTS was higher among patients with chronic postthrombotic vein changes (RR 2.7; 95% CI, 1.2539–5.814; *P*=0.01) and deep venous reflux (RR 2.369; 95% CI, 1.0714–5.2391; *P*=0.03). On the other hand, no significant correlation was detected between thrombosis recurrence and PTS (RR 1.42; 95% CI, 0.4109–4.9668; *P*=0.57). Subgroups analysis also revealed increased risk of thrombosis recurrence among patients with residual vein thrombosis (RR 10.72; 95% CI, 1.35–85.33; *P*=0.02) (Fig. 3).

Discussion

PTS is the most common debilitating complication following acute DVT. PTS is characterized by a spectrum of disease severity from chronic leg pain, aching, heaviness, and swelling, to dermatitis, subcutaneous fibrosis, venous claudication, and skin ulceration that substantially impairs the quality of life of affected patients [19].

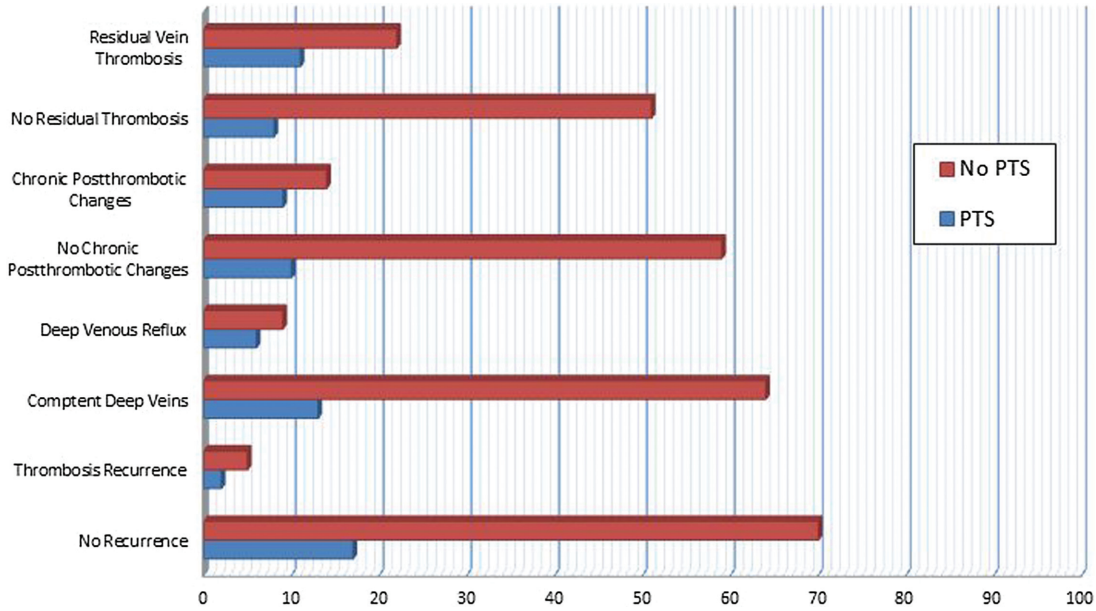
The pathogenesis of PTS is intricate and inadequately understood; it is currently thought that the persistence of thrombus during the initial weeks after an acute DVT leads to PTS by at least two pathways. First, residual thrombus lasting over the long run, even with anticoagulant therapy, physically blocks venous blood flow [20]. Second, the inflammatory response to acute thrombosis is a result of cytokines secreted by leukocytes, growth factors, and proteases that damage venous valves, provoking reflux, and venous hypertension [21].

For many years, in the open vein hypothesis, it has been assumed that rapid thrombus elimination and restoration of unobstructed deep venous flow may prevent valvular reflux, venous obstruction, and PTS; however, in the review of literature, there is a controversy between trials about the validity of this hypothesis [22].

In this randomized controlled study, we observed significant differences in the prevalence of PTS between treatment groups; adjuvant CDT did show a benefit over standard treatment for the prevention of PTS 12 months after acute iliofemoral deep-vein thrombosis (*P*=0.024). PTS severity was evaluated in the two groups and CDT did reduce the severity of the PTS.

Comparing our findings to other studies showed that interventional treatment of iliofemoral DVT has always been controversial and randomized controlled trials (RCT) [Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion (TORPEDO), catheter-directed venous thrombolysis (CaVent), acute venous thrombosis: thrombus removal with adjunctive

Figure 3



Incidence of the postthrombotic syndrome (PTS) in study subgroups according to duplex ultrasound findings.

catheter-directed thrombolysis (ATTRACT), Ultrasound-accelerated catheter-directed thrombolysis versus anticoagulation for the prevention of postthrombotic syndrome (CAVA)] [23–26] have not fully settled the issue of thrombus removal.

In a single-center RCT (the TORPEDO Trial) by Sharifi *et al.*, CDT was superior to anticoagulation alone at 6 months follow-up in preventing PTS (3.4 vs. 27.2%, P=0.001) and recurrent VTE (2.3 vs. 14.8%, P=0.003). However, the follow-up period was short and a validated measure of PTS was not used [23].

Supporting our results, the CaVenT study reported a significant reduction in PTS after additional CDT compared with conventional treatment alone with an absolute risk reduction of 14·4% at 24 months, CaVent also demonstrated an absolute risk reduction of 28.2% (95% CI, 9.7%–46.7; P=0.004) at five years in the interventional group [24,27].

On the other hand, dissimilar results were described by ATTRACT trial; they had concluded that the addition of pharmacomechanical CDT did not lower the risk of PTS at 24 months but resulted in a greater risk of major bleeding [25]. However, an iliofemoral subgroup analysis of ATTRACT suggested that Pharmacomechanical catheter-directed thrombolysis (PCDT) revealed greater relief in leg pain and swelling (P<0.01), diminuted PTS severity (P<0.01) at 6, 12, 18, and 24 months, and reduced incidence of moderate-or-severe PTS (P=0.021) [28].

Comparable to ATTRACT trial, the authors of the CAVA trial noted that additional ultrasound-assisted CDT does not change the risk of PTS at 12 months after acute iliofemoral DVT compared with standard therapy alone [26].

Despite being the largest randomized controlled trial on the role of PCDT in PTS prevention, ATTRACT trial received criticism regarding the inter-observer variability, the enrollment criteria, slow recruitment, and patient loss during follow-up [29]. In ATTRACT trial, recruiting patients with isolated femoropopliteal DVT (47% of study cases) may have influenced the outcomes negatively, as conservative treatment is expected to perform effectively in these patients, consequently diminishing statistically the beneficial effects of thrombolysis on iliofemoral DVT., supporting that, the subgroup analysis of ATTRACT trial revealed significant correlation between post-PCDT residual thrombus and diminished PTS severity over 2 years and lower moderate-or-severe PTS (only 8%) of iliofemoral DVT patients [30].

Another remark on ATTRACT trial, that we avoided in our study, is the inclusion of patients with ipsilateral previous DVT as those patients may have a subclinical valvular reflux or chronic postthrombotic vein changes that would aggravate the severity of recurrent thrombosis. Furthermore, there are questions we raised along with other investigators about the cause of the refusal of a large number of patients (1100 patients, 61% of patients fulfilled study criteria) to participate in the ATTRACT study, many of whom could have severe symptoms and rejected randomization [31].

In spite of escaping a major flaw in ATTRACT trial by recruiting only patients with first-time iliofemoral deep-vein thrombosis, the CAVA trial still has some weaknesses. Actually, the inclusion of only 152 patients after induction of the study in 15 centers for seven years was disappointing. Inquiries have been raised by many authors about the low rate of technical success in the CAVA trial, as CDT was terminated early in 22 (30%) of 74 patients because of no progress in thrombus lysis, and about the high rethrombosis rate that was detected in 14 (18%) of 77 patients within one year follow-up suggesting suboptimal thrombus clearance. Both high procedure failure and rethrombosis could alter the effectiveness of CDT in PTS prevention [32].

Assessment of duplex ultrasound finding in both groups of this study disclosed a significant decline of residual vein thrombosis, chronic postthrombotic vein changes, and deep venous reflux in patients who received CDT compared with standard treatment patients, on the other hand, incidence of DVT recurrence was comparable in the two groups. Subgroups analysis of our study showed a significant correlation between PTS and deep venous reflux, residual vein thrombosis, and chronic postthrombotic vein changes. DVT recurrence was not associated with higher PTS incidence, but it was significantly increased in patients with six months of residual vein thrombosis.

Both CaVent and ATTRACT trials reported lower postprocedure thrombus volume, however in ATTRACT trial this was not associated with lower PTS incidence but was associated with reduced 24-month PTS severity in the iliofemoral DVT subgroup.

Improved iliofemoral patency after 6 months was detected in CDT patients of the CaVent trial compared with control group (P=0.012), similar to our results improved 6 months patency was associated with an absolute risk reduction of PTS by 24.4% (P=0.001).

Unlike PCDT in ATTRACT and CAVA trials, CDT in our study and in CaVent did reduce valvular reflux, the reasons for the differences in the effect of both catheter interventions upon valvular reflux are unknown. Although both interventions revealed immediate postprocedure low thrombus burden, however, there is a possibility that the use of mechanical thrombectomy devices for PCDT may cause macroscopic or microscopic vein wall and valve injury, another possibility is that thrombolysis for a longer period of (e.g. the 48 h in our study vs. the 20 h in ATTRACT) may be associated with more efficient thrombus clearance contributing to normal vein function restoration.

Supporting our results, Haig *et al.* [33] reported an absolute risk reduction of deep venous reflux after 6 months and 24 months in the CDT arm compared with controls, furthermore, they concluded that lack of patency and venous reflux at 6 months were predictors of PTS. Comparable to our findings, Du *et al.* performed a meta-analysis on three RCTs and 3 nonrandomized studies and summarized that, Compared with anticoagulation treatment, additional CDT was associated with a lower rate of PTS and a higher rate of 6-month patency. In addition, CDT did not reduce DVT recurrence, mortality or PE [34].In this study, the incidence of major bleeding was comparable between the two groups. Dissimilar results were reported in ATTRACT trial, as a higher risk of major bleeding within 10 days was detected in the PCDT group (six patients; 1.7%), as compared with one (0.3%) patient assigned to the control group (P=0.049)., however, we think that this conclusion should be revised as a reanalysis of these figures (6/336 patients vs. 1/355 patients) did not reveal a statistical significance between the two groups (P=0.08). In a meta-analysis by Wang *et al.* [35], they noticed that most bleeding complications were puncture-related and mainly due to repeated puncture trials and recommended US-guided access to reduce the chance of iatrogenic arterial injury, as well as using the smallest possible vascular sheath.

In this study, stent placement was limited to patients with anatomical venous stenosis as in May–Thurner syndrome; however, the indications of stent placement after CDT may be controversial. Fleck *et al.* [3] reported that stenting may be useful in patients with venous stenosis or with anatomic risk factors for clot formation such as in May–Thurner syndrome, on the other hand in a study by Engelberger *et al.* [36] they concluded that routine stenting for residual thrombosis after CDT was associated with high patency rates and low incidence of PTS. Conflicting results by CAVA reported that venous stenting was complicated by a high proportion of in-stent thrombosis [26].

According to the European society for vascular surgery, there are no trials conducted direct comparison between stenting and no stenting following early thrombus removal, furthermore, there is no evidence to support one protocol over another for poststenting anticoagulation, moreover, the deep venous stenting optimum anticoagulation regimen remains controversial and further studies are still required [6].

The limitations of our study include the shorter follow-up period (12 months) compared with other RCTs; the need for frequent follow-up visits to maintain INR within a therapeutic range which created an overburden on patients and physicians; longer hospital stays faced in this study. Therefore, further research in multiple high-flow centers are needed to investigate not only the role of CDT in proximal DVT but also other factors, for example, biological or inflammatory markers that can modify its efficacy.

In conclusion, among patients with first-time acute proximal deep-vein thrombosis, the addition of CDT to anticoagulation resulted in a lower risk of PTS. CDT led to reduced late residual thrombus burden, chronic postthrombotic vein changes, and deep venous reflux. Duplex ultrasound changes including deep venous reflux, residual vein thrombosis, and chronic postthrombotic vein changes can be considered predictors for PTS.

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Conflicts of interest
There are no conflicts of interest.

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