Health-related quality-of-life improvement using catheter-directed thrombolysis for iliofemoral deep venous thrombosis

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Purpose
Catheter-directed thrombolysis (CDT) effectively eliminates thrombus in patients with iliofemoral deep vein thrombosis (DVT) with good patency and low complication rates. Thus, an effective measure of treatment success is the assessment of health-related quality of life (HRQOL). This study evaluates whether CDT for iliofemoral DVT is associated with improved HRQOL compared with standard anticoagulation (AC) treatment.
Patients and methods
Between January 2016 and June 2017, 33 (33 limbs) patients having acute iliofemoral DVT were allocated in two groups: group A (18 patients) received standard AC therapy alone and group B (15 patients) was managed with CDT. All patients were candidates for thrombolysis. Follow-up included clinical exanimation and ultrasound. Mean age was 32.6 years (19–57 years) in group A and 34.2 (20–53), in group B. The percentage of male and female was 38.8 and 61.2%, respectively, in group A and 33.3 and 66.4%, respectively, in group B. The venous clinical severity score and the modified Arabic version of the Chronic Venous Insufficiency Questionnaire 20 questionnaires were used to assess the quality of life and symptoms of post-thrombotic syndrome.
Results
Thrombus lysis was completed in 10/15 (66.6%) patients, partial in four (26.6%) patients, and not achieved in one (6.6%) patient. Successful CDT was followed by stent angioplasty in 33.3% (5/15) of the patients. There was significant difference between the two patient groups regarding Chronic Venous Insufficiency Questionnaire 20 questionnaire at 1 and 12 months, with *P* value of 0.01. Moreover, venous clinical severity scores at 6 and 12 months were statistically different between the two groups, with *P* values of 0.005 and 0.009, respectively.
Conclusion
CDT for the management of patients with iliofemoral DVT significantly improves HRQOL compared with similar patients treated with AC alone. Improved quality of life is related to successful thrombolysis.

Keywords:
catheter-directed thrombolysis, deep venous thrombosis, health-related quality-of-life

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Introduction

Deep venous thrombosis (DVT) of the lower extremity is a major health problem associated with significant morbidity and mortality. DVT is reported to occur in ~50.4/100 000 person annually [1], with 1-year mortality of ~14.6% [2]. In particular, untreated iliofemoral DVT may be complicated with pulmonary embolism (PE), of which there is a 10% risk of mortality within 1 h of symptom onset [3].

DVT may cause severe short-term morbidity from PE and phlegmasia caerulae dolens or venous gangrene and in the longer-term from post-thrombotic syndrome (PTS). PTS is a common problem resulting from chronic venous insufficiency characterized by pain, edema, venous claudication, and skin changes, which can progress to venous ulceration, despite anticoagulation (AC) therapy [4]. PTS affects approximately half of the patients within the first 1–2 years of a DVT episode, of which 5–10% experience severe PTS (venous ulcer) [5]. It causes significant disability, impaired quality of life (QOL), and economic burden on healthcare system [6].

Previous studies have mainly focused on immediate treatment results, complications, and recurrent thrombosis. Lately, focus has turned toward the effect of PTS on QOL as another treatment outcome assessment, and recent research has shown

that QOL among patients with PTS is poor [7]. Standardized instruments assessing QOL have been developed such as the Villalta scale [8], Chronic Venous Insufficiency Questionnaire 20 (CIVIQ) [9], and venous clinical severity score (VCSS) [10].

Patients and methods

Study design

A prospective simple nonrandomized clinical trial was conducted, where 33 eligible patients with iliofemoral DVT were recruited and allocated into two matched groups: group A (18 patients) received new oral ACs (rivaroxaban 15 mg twice daily was started for 21 days followed by maintenance dose of 20 mg once daily) and group B (15 patients) was treated with catheter-directed thrombolysis (CDT). The study was conducted at the Department of Vascular Surgery, Zagazig University, Egypt. After CDT, all patients were treated with graduated compression stockings class II (18–24 mmHg) and 1 year of AC therapy.

Inclusion criteria

First episode of iliofemoral DVT, ambulatory patients less than 60 years old, with life expectancy more than 1 year, and duration of thrombus of maximum of 14 days. Written informed consents of all patients were obtained for participation after full explanation of risks and benefits of treatment.

Exclusion criteria

Previous ipsilateral DVT; contraindications to thrombolytic therapy including active internal hemorrhage, cerebrovascular accident within previous 2 months, recent major trauma or surgery less than 14 days, recent gastrointestinal bleeding, severe hypertension (>180/100), pregnancy, lactation or delivery within the past 20 days, malignant disease requiring chemotherapy, acute pancreatitis, hepatic failure, severe renal failure, coagulopathy, and thrombocytopenia (platelets<100/dl); and drug abuse or mental disease that may interfere with compliance of treatment and follow-up.

Technique of catheter-directed thrombolysis

With the patient in prone position, ultrasound-guided puncture of the ipsilateral popliteal vein of the affected limb was done. A hydrophilic guide wire was inserted and advanced through the whole length of the thrombus. A 5-F vascular sheath was then inserted through which all subsequent catheter and wire exchanges were performed. After that, contrast material was injected through the sideway of the vascular sheath to document the thrombus, to determine its distal extent, and to visualize collaterals. Infusion catheter (Fountain Infusion systems, Merit Medical Systems Inc., Utah, USA) with multiple side holes was placed in the thrombus, and infusion was started as follows: a loading dose of 15-mg Actilyse (rt-PA; Boehringer Mannheim, Germany) was injected manually as three doses, each of them 5 mg at 10-min intervals. Actilyse was then infused into the thrombus at a rate of 1 mg/h with the aid of an infusion pump over a period of maximum of 72 h. Standard unfractionated heparin was injected simultaneously in the side arm of the vascular sheath at a fixed rate of 500 IU/h, and the dosage was adjusted according to the partial thromboplastin time value (1.5 normal value). Progression of lysis was controlled by venography every 24 h. The treatment was stopped in any case if no residual thrombotic material was visible or if no further lysis was observed between two consecutive venographies. Any residual stenosis in the iliac vein was treated with stent placement. During thrombolytic therapy, the patient was rested in bed in intensive care unit for close observation to detect any evidence of hemorrhagic complication. Removal of the vascular sheath was done 12 h after cessation of the thrombolytic infusion; care was taken with the final removal owing to high risk of local extravasation and hematoma. After the procedure, low-molecular-weight heparin was given for 72 h; after which, rivaroxaban 15 mg twice daily was started for 21 days followed by maintenance dose of 20 mg once daily.

Complications

Any complications including minor or major hemorrhage and PE were recorded.

Follow-up

Follow-up included clinical examination and duplex ultrasound imaging where deep venous patency and function were assessed at 6 and 12 months. All patients were asked to complete the modified Arabic version CIVIQ_20 questionnaire at 1 and 12 months and VCSS questionnaire at 1, 6, and12 months.

Duplex ultrasound three criteria were used for comparison between the two study groups: vein lumen, collateralization, and vein valve function (Tables 1–4).

Quality of life assessment

Validated questionnaires in the form CIVIQ_20 and VCSS were used.

Chronic venous insufficiency questionnaire

It is short, consisting of only 20 questions. It emphasizes four dimensions: psychological, pain, physical, and social function. CIVIQ_20 does not sufficiently emphasize the specific anatomic and

Table 1 Duplex ultrasound criteria

Vein lumen comparison with other side	Normal	Reduction <25%	Reduction 25–50%	Reduction >50
Collateralization	Absent	Mild	Moderate	Severe
Venous valve function (reflux)	Normal	Mild	Moderate	Severe
	0	1	2	3

Table 2 Demographic information by treatment group

Characteristics	Conservative group (*N*=18)	Catheter-directed thrombolysis group (*N*=15)	*P* value
Sex			
Male	7	5	0.109
Female	11	10	
Age (years)	32.6 (19–57)	34.2 (20–53)	0.769
Limbs with deep vein thrombosis			
Left	14	11	0.088
Right	4	4	
Iliofemoral	17	13	0.599
Iliac	1	2	

Table 4 Duration of thrombolysis in relation to duration of deep vein thrombosis in catheter-directed thrombolysis group

	Duration of thrombolysis [*n* (%)]	<7 Days deep vein thrombosis [*n* (%)]	8–14 days deep vein thrombosis [*n* (%)]
24 h	4 (26.67)	2 (50)	2 (50)
48 h	9 (60)	5 (55.6)	4 (44.4)
72 h	2 (13.33)	1 (50)	1 (50)

physiologic issues of severe cardiovascular disease. It is limited to certain objective findings and subjective symptoms, some of which are vague (Figs 1–8).

Statistical analysis

Data were analyzed using SPSS statistics, version 23 (SPSS Corp., Armonk, New York, USA). *P* value was considered statistically significant if less than 0.05. Categorical variables were compared using Fisher's exact and χ^2-test and numeric data were compared using independent sample *t*-test.

Results

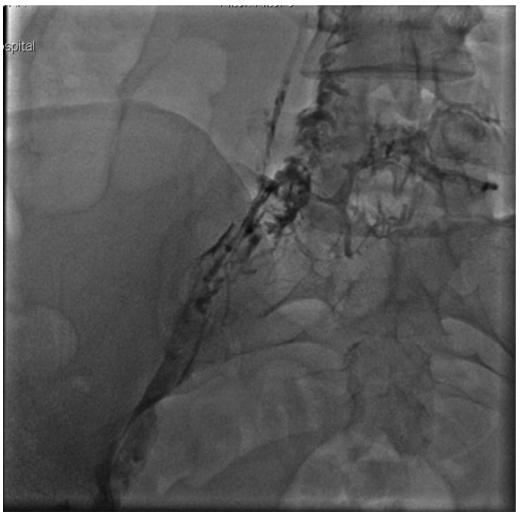
The demographic data are demonstrated in Tables 5 and 6, showing no significant difference between the groups: 18 patients were recruited in the conservative group and 15 patients were recruited to the CDT group.

Treatment outcome in the CDT group was as follows: 10 (66.7%) patients achieved complete lysis, four (26.7%) patients had partial lysis, and one (6.6%)

Table 3 Treatment outcomes in 15 patients treated with catheter-directed thrombolysis

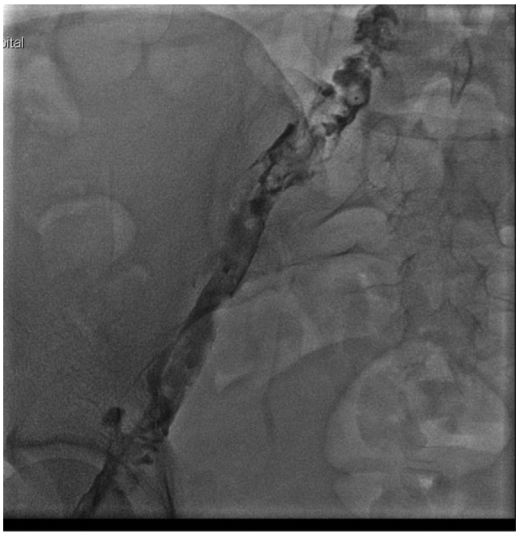
Lysis of thrombosis	*n* (%)
Grade I (<50% lysis)	1 (6.67)
Grade II (50–99% lysis)	4 (26.67)
Grade III (100% with no residual clot)	10 (66.67)
Stented limbs	5 (33.33)

Figure 1



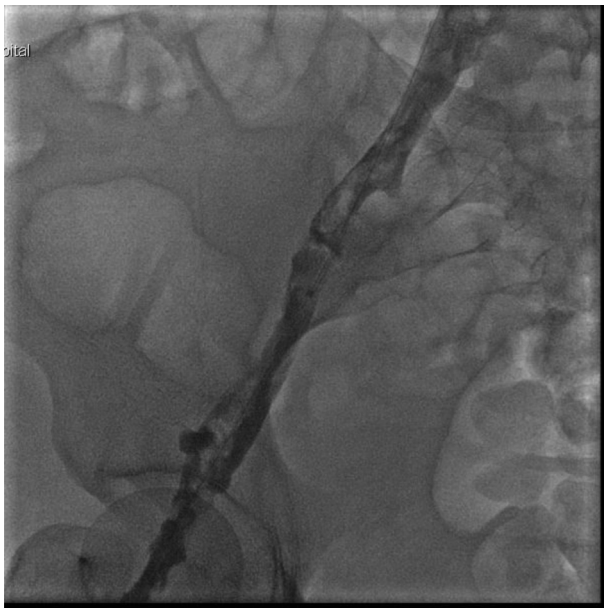
External iliac vein before thrombolysis.

Figure 2



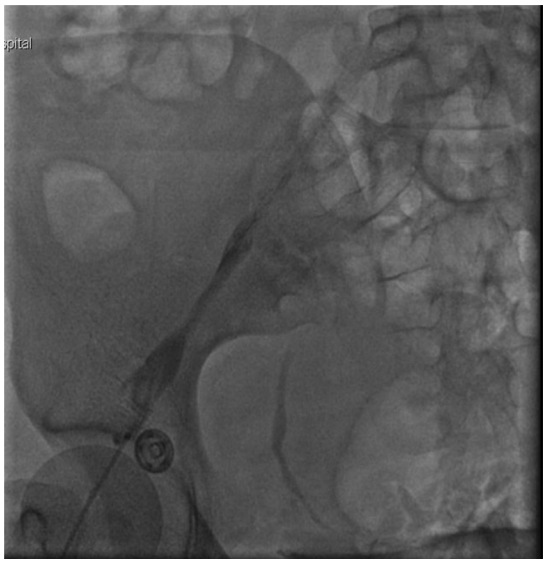
External iliac vein 24 hours after beginning thrombolysis.

Figure 3



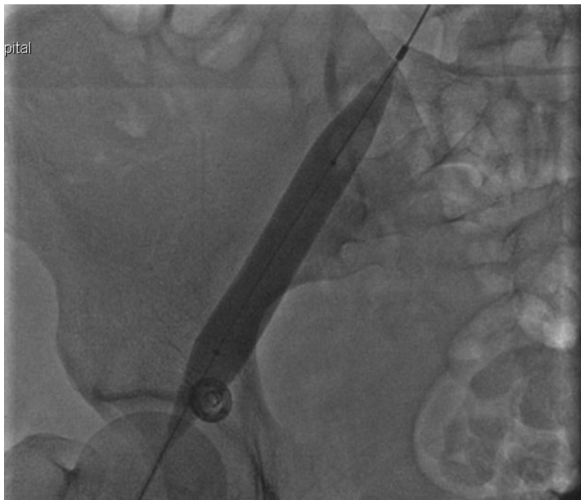
External iliac vein 48 hours after the beginning of thrombolysis.

Figure 4



External iliac vein stenosis.

Figure 5



External iliac balloon dilatation.

patient showed poor lysis, most probably owing to delayed presentation.

Achieving venous patency

A three-point scale has been proposed to define outcomes of therapy for DVT, with grades II and III signifying at least 50% luminal patency after the procedure, and this was considered a satisfactory therapeutic outcome [11].

Duration of lysis in relation to the duration of the DVT showed no significant difference. There were two cases of minor sheath site bleeding controlled by compression and one case with major retroperitoneal hemorrhage, which warranted stoppage of lysis after 40 h and blood transfusion was needed. No PE occurred in any of our cases in both groups.

In the conservative group, three patients failed to attend the 6 and 12-month follow-up, whereas in the CDT group, two patients failed to attend the follow-up as well, and these were considered as missed values in our statistical analysis.

The VCSS score at 1 month showed no significant difference between the groups. At 6 and 12 months, the VCSS score showed significant difference in favor of the CDT group.

The global index score for the CIVIQ20 questionnaire at 1 and 12 months showed significant difference in favor of the CDT group.

As shown in Table 7, duplex ultrasound follow-up of both groups showed significant difference between the two groups regarding reflux at 6 and 12 months.

Tables 8 and 9 showed that vein lumen patency was significantly better in the CDT group at both 6 and 12 months, and the CDT group showed significantly less formation of collateralization at both 6 and 12-month duplex ultrasound follow-up.

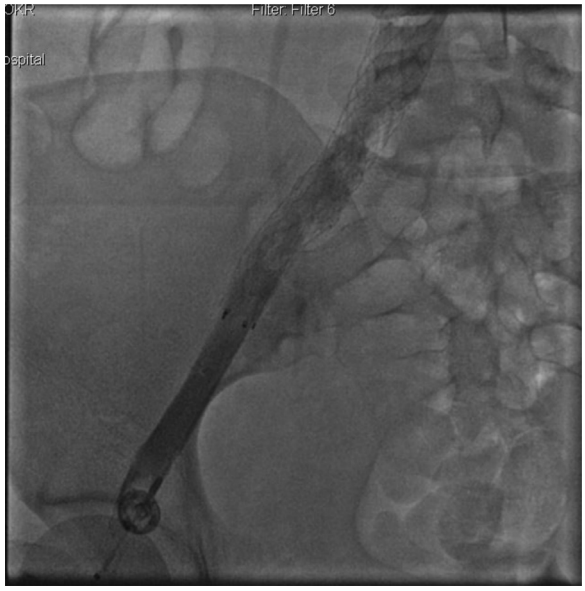
Discussion

The iliofemoral venous segment is the single venous outflow channel of the lower extremities. When it becomes occluded with thrombus, patients' symptoms are usually severe. This causes an acute increase in venous and compartmental pressures, which often persist as chronic venous hypertension which is the basic pathophysiology of post-thrombotic morbidity [12].

Spontaneous recanalization of iliofemoral DVT is very poor with AC alone. Approximately 20% of these iliac veins will completely recanalize on AC treatment, and the remaining veins recanalize partly and develop varying degrees of obstruction and collateralization [13]. Compared with AC alone therapy, CDT plus AC was demonstrated to be more effective for dissolving venous thrombus; however, in the recent guidelines for acute proximal DVT of the leg, AC treatment alone is still recommended over CDT, and the evidence grade is not high (2C) [14].

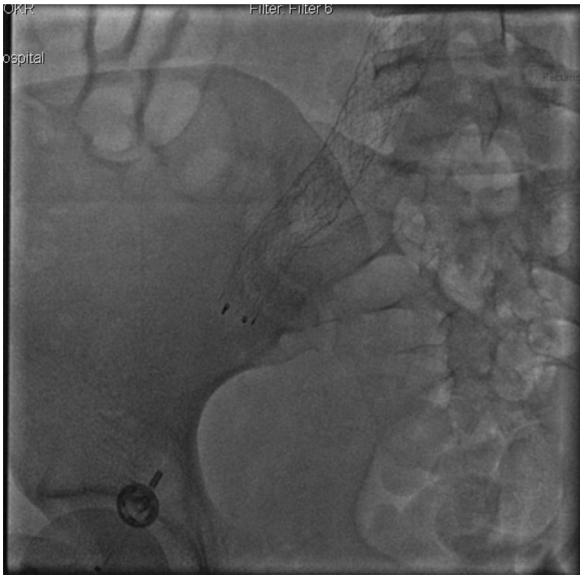
The meta-analysis of Lu *et al.* [15], that included 10 studies, four of them were RCT, compared

Figure 6



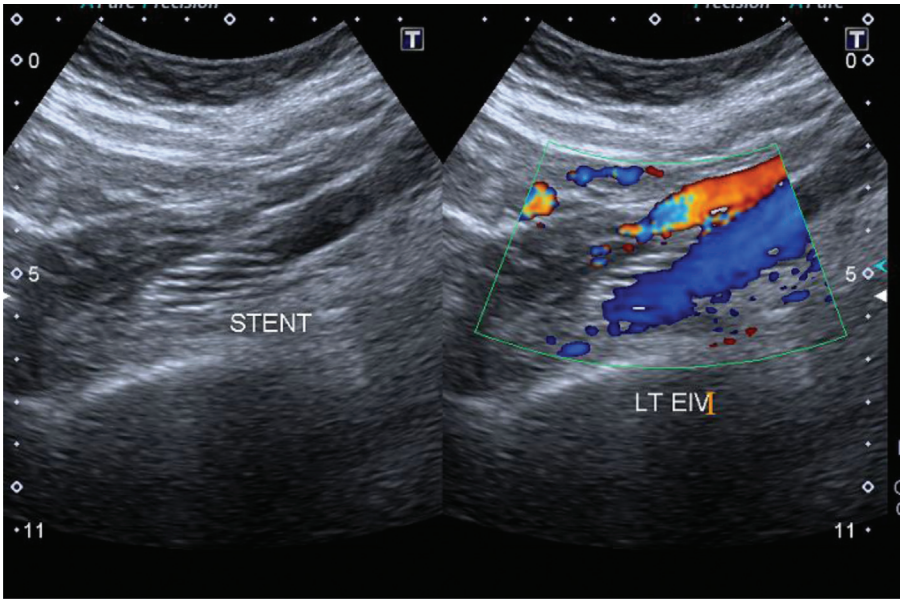
External iliac stenting with contrast.

Figure 7



External iliac stent without contrast.

Figure 8



Colored duplex of the external iliac vein after stenting.

CDT plus AC versus standard AC for acute iliofemoral DVT, and it demonstrated that CDT improved the patency of the iliofemoral vein and decreased the severity of PTS compared with AC therapy alone, while demonstrating that PTS incidence remains debatable. However,

Table 5 Venous clinical severity score independent sample *t*-test between our two groups of patients

	Conservative group mean	CDT group mean	*t*	*P*
VCSS 1 month	13.5	10.6	1.433	0.162
VCSS 6 months	13.7	9.2	3.029	0.005
VCSS 12 months	13.56	7.87	4.341	0.009

CDT, catheter-directed thrombolysis; VCSS, venous clinical severity score.

Table 6 Global index score for the Chronic Venous Insufficiency Questionnaire 20 questionnaire using independent sample *t*-test between the two groups of patients

	Conservative group mean	CDT group mean	*t*	*P*
CIVIQ20 questionnaire 1 month	54.94	33.60	3.495	0.01
CIVIQ20 questionnaire 12 month	51.00	15.27	7.706	0.011

CDT, catheter-directed thrombolysis; CIVIQ, Chronic Venous Insufficiency Questionnaire.

Table 7 Reflux at 6 and12 months in duplex ultrasound follow-up of both groups

	Conservative group	CDT group	Total	*P* value for Fisher exact test
Reflux at 6 months				
None	2 (22.2)	7 (77.8)	9 (100)	0.03
Mild	9 (60.0)	6 (40.0)	15 (100)	
Moderate	4 (100.0)	0 (0)	4 (100)	
Reflux at 12 months				
None	1 (12.5)	7 (87.5)	8 (100)	0.02
Mild	5 (50)	5 (50)	10 (100)	
Moderate	7 (87.5)	1 (12.5)	8 (100)	
Severe	2 (100)	0 (0)	2 (100)	

CDT, catheter-directed thrombolysis.

Table 8 Vein lumen at 6 and 12 months in duplex ultrasound follow-up of both groups

	Conservative group	CDT group	Total	*P* value for Fisher exact test
Vein lumen 6 months				
Missing	3 (60)	2 (40)	5 (100)	0.002
Normal	1 (10)	9 (90)	10 (100)	
Reduction<25%	4 (57.1)	3 (42.9)	7 (100)	
Reduction 25–50%	6 (85.7)	1 (14.3)	7 (100)	
Reduction>50%	4 (100)	0 (0)	4 (100)	
Vein lumen 12 months				
Missing	3 (60)	2 (40)	5 (100)	0.001
Normal	2 (15.4)	11 (84.6)	13 (100)	
Reduction<25%	8 (80)	2 (20)	10 (100)	
Reduction 25–50%	5 (100)	0 (0)	5 (100)	

CDT, catheter-directed thrombolysis.

Table 9 Collateralization at both 6 and 12-month duplex ultrasound follow-up

	Conservative group	CDT group	Total	*P* value for Fisher exact test
Collateralization at 6 months				
Missing	3 (60)	2 (40)	5 (100)	0.007
None	3 (23.1)	10 (76.9)	13 (100)	
Mild	11 (78.6)	3 (21.4)	14 (100)	
Moderate	1 (100)	0 (0)	1 (100)	
Collateralization 12 months				
Missing	3 (60)	2 (40)	5 (100)	0.002
None	1 (10)	9 (90)	10 (100)	
Mild	11 (73.3)	4 (26.7)	15 (100)	
Moderate	2 (100.0)	0 (0)	2 (100)	
Severe	1 (100)	0 (0)	1 (100)	

CDT, catheter-directed thrombolysis.

substantially more bleeding and PE events occurred in the CDT group.

In our study, we followed the commonly used regimen regarding actilyse infusion (15 mg initial bolus dose followed by infusion rate at 1.0 mg/h). This was consistent with the standard doses used in the CaVenT [16] and ATTRACT [17] trials, which are two of the most important clinical trials regarding the value of CDT for acute DVT treatment that used a dose of 0.01 mg/kg/h not to exceed 1.0 mg/h of actilyse continuous infusion.

We did not find significant difference in duration of thrombolysis in patients presenting during the first week of symptoms onset and those presenting after that regarding the final lysis grade or complication rates. Unfortunately, no studies revealed the effect of early (<7 days) versus late (8–14 days) CDT on success of lysis or development of PTS.

Regarding the achievement of luminal patency, we observed more than 50% of venographic primary success in 93.3% (14/15) of patients compared with 65.9% in CaVenT trial. This is owing to the small size of our study. Moreover, the venous patency is maintained in CDT group during 6 and 12 months at duplex follow-up with significant difference ($P>0.05$) between two groups. This also indicated that better luminal patency is associated with less venous collateralization in CDT group at 12 months ($P=0.002$).

There was significance difference in deep venous valvular reflux between the two groups at 6 and 12 months. Valvular competence was preserved in 40% of patients treated with CDT compared with 72% of those treated with systemic AC ($P=0.02$), which is comparable to Laihoa *et al.* [18] who stated deep vein reflux was present in 44% of catheter-directed lysis-treated patients compared with 81% of the systemic-treated patients ($P=0.03$, χ^2). Moreover, Elsharawy and Elzayat [19] demonstrated that venous reflux was higher in patients treated with AC versus CDT ($P=0.042$).

The complication rate seems to be low with 3/15 (20%) of all procedures, namely, puncture site bleedings ($n=2$) without any need of blood transfusions. Only one case developed major retroperitoneal bleeding that necessitated stoppage of lysis therapy after 40 h with the need of blood transfusion.

Concerning the QOL assessment, our follow-up of 12 months was inferior to the 24 months of CAVENT trial. Comparing the results of the two used HQOL questionnaires, namely, CIVIQ-20 and VCSS, at 12-month follow-up, patients treated with CDT plus AC showed normal values within the two different scoring systems, indicating a normal QOL.

CIVIQ-20 scores at 1 and 12-month follow-up were 54.94 and 51.00, respectively, in conservative group and 33.60 and 15.27, respectively, in CDT groups. The difference was significant in CDT group ($P<0.05$). Zhang *et al.* [20] showed no significant difference between the two groups using CIVIQ-20 questionnaire with mean scores (20.2±14.4 and 16.6 ±11.0 in AC and CDT groups, respectively) ($P>0.05$), but it was lower in CDT group than AC group.

In comparing QOL improvement to the degree of lysis, Grewal *et al.* [21] divided patients treated with CDT or pharmacomechanical procedures in two groups according to their degree of clot lysis (above and below 50% lysis). The Physical Component Summary was significantly higher ($P=0.35$) in patients with more than 50% lysis compared with the other group. This was comparable to our results using CIVIQ-20 questionnaire, as more than 90% of our patients achieved more than 50% lysis.

In general, all available studies evaluating the QOL improvement are not able to estimate, if an improved QOL may be the result of CDT compared with conservative treatment as a therapeutic strategy in case of acute DVT. It is important to mention the fact that the follow-up periods of all available studies, which were used to evaluate the benefit of CDT to prevent PTS, were short regarding the normal course of PTS.

Limitations

Our trial had several limitations. There were occasional missed visits among patients who returned for follow-up. The follow-up duration was not sufficient for the development of PTS in its full picture with its great effect on QOL assessment. Furthermore, the small number of patients included ($n=33$) may be a potential explanation of these findings

Conclusion

CDT appeared to be safe and feasible and showed good patency rates. Additional stent angioplasty of the iliac veins, which is necessary in cases with iliac stenosis, after CDT was associated with good venous patency

without an increased complication rate. Patients treated with CDT for their iliofemoral DVT at the acute event had significantly improved HQOL owing to preservation of venous patency and venous valve functions at 12-month follow-up and that patients with patent deep veins and sufficient valves have higher QOL scores than patients with reflux and occluded veins.

Although CDT is feasible with good patency rates, further prospective randomized long-term trials are necessary to evaluate the value of thrombus removal in iliofemoral DVT in comparison with conservative treatment considering QOL improvement.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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