Catheter-directed thrombolysis vs pharmacomechanical catheter-directed thrombolysis in acute iliofemoral deep vein thrombosis

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Purpose
The aim was to compare the effectiveness of catheter directed thrombolysis (CDT) and pharmacomechanical catheter-directed thrombolysis (PCDT) in the treatment of acute, massive iliofemoral deep vein thrombosis.
Patients and methods
A prospective study was conducted on 50 patients in Zagazig University Hospitals between March 2014 and April 2018. The patients were randomized into two groups. Group A underwent CDT and group B underwent PCDT (ASPIREX). Primary end points were venous patency, complication rate, patient satisfaction, and quality of life Chronic Venous Insufficiency Questionnaire-20. Secondary end points were recurrence and occurrence of post-thrombotic syndrome (PTS), (the Villalta score and revised Venous Clinical Severity Score) within 24 months.
Results
Aspirex was successful in the majority of patients and grade III, II, and I thrombolysis was achieved in 56, 32, and 12% of patients, respectively, while in the CDT group of patients achieved 44, 36, and 20%, respectively. Recanalization was achieved in 88% patients. At 24 months 32% patients who received CDT presented with PTS compared with 20.83% in the PCDT group after exclusion of one patient who died. Three cases of severe PTS were reported in the CDT group. There was statistically significant difference in PTS at 6 months between the two groups. When comparing Chronic Venous Insufficiency Questionnaire-20 scores between the two groups, there was statistically significant difference between them at 6, 12, and 24 months with more improvement in Aspirex group.
Conclusion
Aspirex is an effective treatment for lower limb deep vein thrombosis, and the clinical results achieved were superior in comparison with CDT alone.

Keywords:
CTD, deep vein thrombosis, pharmacomechanical thrombectomy

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Introduction

Acute deep vein thrombosis (DVT) occurs in about two cases/1000 persons in the general population [1]. DVT is a rapid, progressive disease with many complications, such as pulmonary embolism and post-thrombotic syndrome (PTS). In spite of the use of proper anticoagulation in full dose and to enough periods (to achieve complete recanalization) (about 6 months) many patients develop PTS [2].

PTS occurs in 24–45% of patients with DVT [3] and manifested by lower limb edema, heaviness, skin hyperpigmentation, secondary varicose veins, and venous ulcers [4], with severe decline in health-related quality of life (HR-QOL) [5].

The main task of traditional anticoagulation is not thrombolysis, so many surgical, chemical, and mechanical strategies have been developed for the removal of thrombus [6].

Catheter directed thrombolysis (CDT) has been used for many years as an effective therapy in some DVT cases because it has rapid thrombolytic effect, with rapid symptomatic relief [7]. However, it carries high risk of bleeding than anticoagulation therapy [8].

Mechanical thrombectomy involves open surgical procedures to remove the clot or percutaneous insertion of a catheter-based device that aspirates or macerates the thrombus. The invasive nature of surgical thrombectomy limits its utilization to patients with limb-threatening DVT [9].

Mechanical thrombectomy with endovascular devices such as rotational wires, saline jet, or ultrasound wave

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were used to disperse the clot, as well as aspiration, because their stand-alone use is not sufficiently effective; mechanical approaches are often used in conjunction with chemical thrombolysis [10].

Pharmacomechanical catheter-directed thrombolysis (PCDT) (Aspirex), which is a combination of mechanical power, aspiration, and use of anticoagulants without using thrombolytic agents, enables a shorter period of intensive-care monitoring with success rates similar to pharmacologic CDT alone [11].

The aim of the current study is to compare the effectiveness of CDT and PCDT in the treatment of acute massive iliofemoral DVT patients.

Patients and methods

This study is a prospective study that was conducted on 50 patients in Zagazig University Hospitals between March 2014 and April 2018. Inclusion criteria were ambulatory patients aged 18–65 years, first-attack iliofemoral DVT with symptom duration of less than 14 days and confirmed by duplex ultrasonography (DUS), and no contraindications to thrombolytic agent or anticoagulants. Exclusion criteria were life expectancy of less than 1 year. Previous DVT, diabetic retinopathy, pregnancy, lactation, hepatic, renal deterioration, uncontrolled hypertension, recent cerebrovascular insult (within 3 months), and recent major surgery or hemorrhage and known allergy to thrombolytic therapy.

It has been assumed that the expected patency rate was 61% in those treated with pharmacologic CDT compared with 92% in those with PCDT. With a significance level of 5% and a statistical power of 80%, 50 patients (25 in each group) must be included in the study. Patients were randomized by simple, computerized randomization into two groups. Group A was treated with pharmacologic CDT and group B was treated with PCDT (ASPIREX, Straub Medical, Wangs, Switzerland).

The technique of thrombolysis used in our trial was the same as the CaVenT study [12,13] (catheter-directed venous thrombolysis in acute iliofemoral vein thrombosis trial). Patients allocated to CDT did not receive warfarin initially but were put on therapeutic subcutaneous low-molecular-weight heparin (LMWH) alone until the start of CDT. LMWH was discontinued the night before and the morning of the procedure.

Standard unfractionated heparin (UFH) (Liquemin, Hoffmann-La Roche, Grenzach-Wyhlen, Germany) was used during the procedure and early postoperative period due to its short half-life and offers better control of the degree of anticoagulation.

At the start of CDT, an intravenous bolus dose of UFH, 5000 Ul, was given. With the patient in prone position, after applying a local anesthetic, an ultrasound-guided puncture of the ipsilateral popliteal vein was performed regardless of whether it was thrombosed or patent. A hydrophilic guide wire, 0.035-inch (Terumo; Medical, Tokyo, Japan), was advanced through the thrombus. A 6-F sheath was inserted. A venogram was obtained to detect the extension of thrombosis. The catheter was placed above the proximal part of the thrombus and another venogram was obtained to confirm patency of venous outflow of the inferior vena cava.

An appropriate-length infusion catheter with multisided holes covering the thrombosed segment and stiffening core (Uni-Fuse; AngioDynamics, Queensbury, NY, USA or Fountaine; Merit Medical Systems, Inc., South Jourdan, Utah, USA) was used. The catheter was advanced and embedded within the main body of the thrombus. The catheter tip-occluding wire is then placed, and infusion of the thrombolytic agent was started as follows: a loading dose of 15 mg Actilyse (rt-PA, Boehringer Mannheim, Germany) was injected manually using a syringe driver 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 72 h.

UFH was injected simultaneously in the side arm of the vascular sheath at a rate of 5–10 U/kg/h to prevent thrombus formation with the dosage adjusted according to the partial thromboplastin time (PTT) (1.5–2.0 times the control value). If two catheters were used in bilateral cases, 0.5 mg/h was administered through each catheter and a divided dose of heparin through the sheaths. Treatment continued in the ICU where vital signs and the puncture site were assessed several times a day. Hematocrit, platelet count, and PTT for the adjustment of heparin dose were monitored every 8 h.

Thrombolysis was assessed daily by venography using a contrast injection through the sheath and/or perfusion catheter. Once partial patency was achieved, the infusion catheter was repositioned within the residual thrombus. The treatment was stopped in

complete recanalization or if no thrombolysis was observed between two venographies. Any residual stenosis in the iliac vein was treated with stent placement. A self-expandable stent (Wallstent; Boston Scientific, Watertown, Massachusetts, USA) of appropriate diameter and length was used. Removal of the sheath was done 6–12 h after cessation of thrombolytic infusion with local compression of the puncture site to avoid extravasation and hematoma formation.

A full dose of LMWH was initiated 1 hour after removal of catheters. Oral anticoagulation was then established. Immediately after CDT, all patients received knee-high elastic compression stockings and were instructed daily wear for 12 months.

In PCDT (ASPIREX) under local anesthesia in prone position, with the ultrasound guidance, a percutaneous 11-Fr sheath was placed in Seldinger technique into the popliteal (Figs 1 and 2), through it contrast venogram was obtained for detection of the distal extent of the thrombus. The thrombosed lesions were traversed with a 0.035-inch guide wire (Terumo, Medical) (Figs 3 and 4). An Aspirex thrombectomy catheter (Straub Medical, Wangs, Switzerland) was introduced till the proximal end of the thrombus. Saline bag was prepared by heparinization of the half of saline volume (5000 IU in 250 ml) and the same volume of contrast was added into the infusion bag. The heparinized saline/contrast bag was put in a pressure cuff (which was inflated to 75 mmHg) and connected through an infusion line with the side port of the introducer sheath.

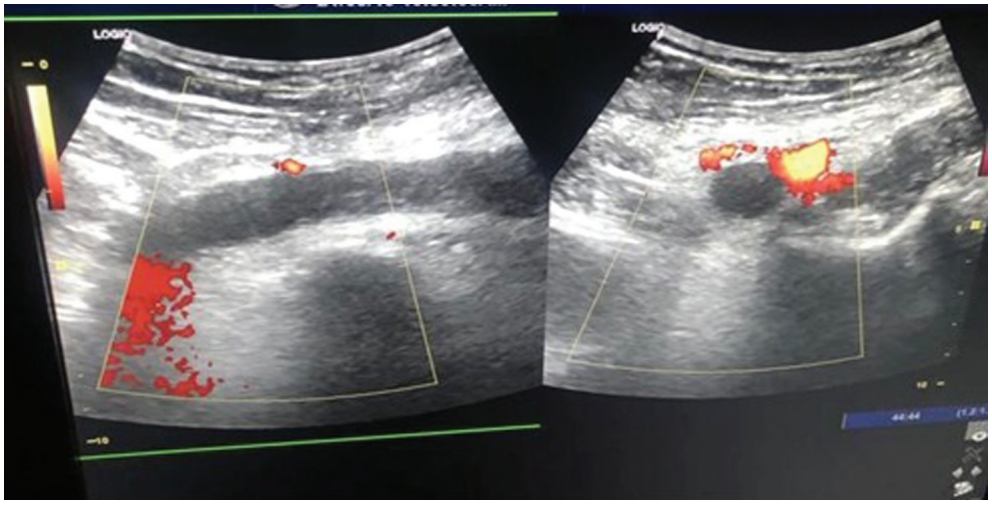
The 10 Fr Aspirex catheter was adjusted into the thrombus after ensuring that the vessel was filled with saline/contrast mix and the pressure was adjusted by using the roller clamp of the infusion line, so that there will be sufficient saline/contrast mix to fill the vessel and make the thrombus visible.

To avoid the systemic effect on the patient, the saline/contrast mix was continuously aspirated by the Aspirex catheter. The roller clamp was used to adapt the volume of the saline/contrast infusion, thus getting the opportunity to open the vein wider or to let the vein collapse a little to get all the thrombotic material aspirated.

Figure 2

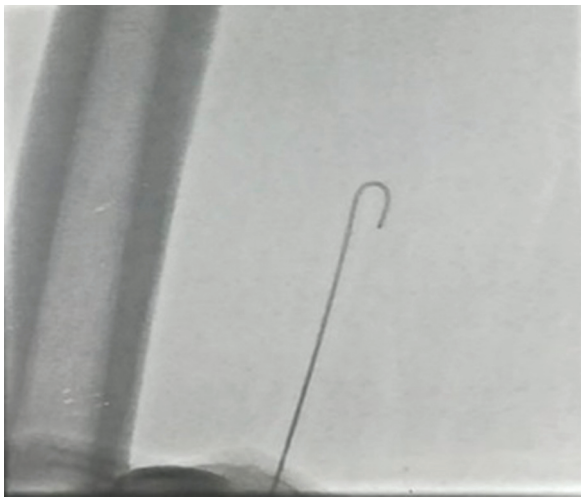
One of the patients in prone position with access of popliteal vein by Seldinger technique.

Figure 1



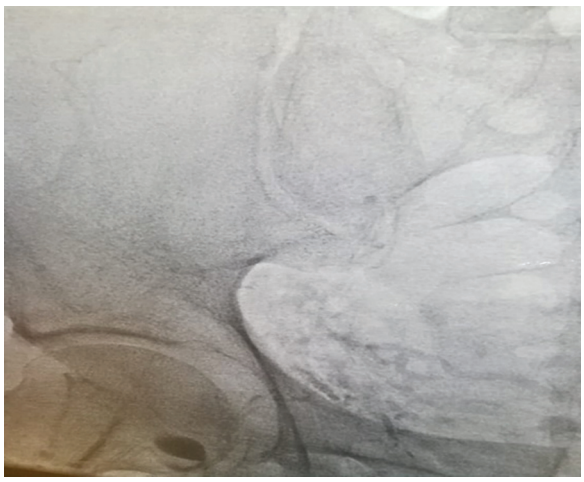
Duplex-guided Seldinger technique for popliteal vein access.

Figure 3



Guide wire inside the popliteal vein.

Figure 4



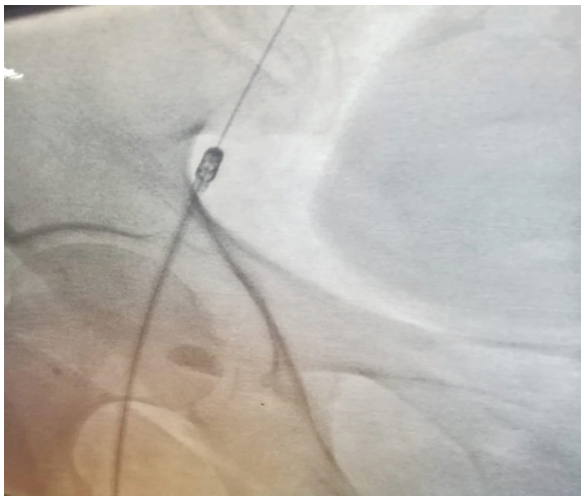
Contrast venogram shows total occlusion of common femoral and iliac veins (no flow).

When the distal thrombus had been reached, we had to keep the catheter running through the thrombus, so it was all aspirated. Working with the saline/contrast mix, the thrombus will be visible in the vessel (Figs 5–9).

The patients were recommended to use oral anticoagulation and use knee-high elastic compression stockings (30–40 mmHg at ankle) daily for 12 months.

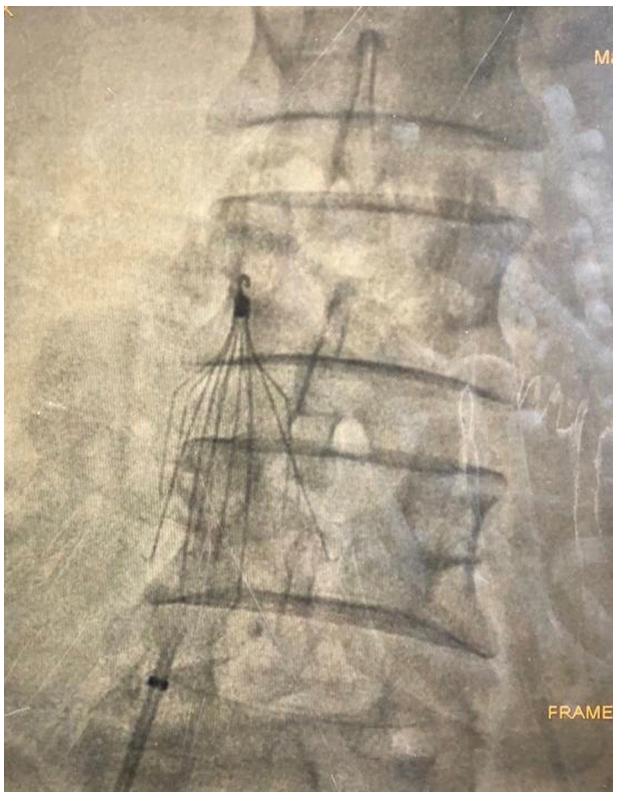
The success of thrombolysis was graded using a well-known scale based on the percentage of thrombolysis achieved Table 1 [14]. Early patency of the deep veins was considered to have been achieved in patients with grade II or grade III thrombolysis on the immediate post? CDT/PCDT venogram. The grade of clot lysis was calculated on the basis of the amount of residual clot at the completion venogram compared with pretreatment venogram.

Figure 5



Aspirex catheter at the level of the head of the femur.

Figure 6



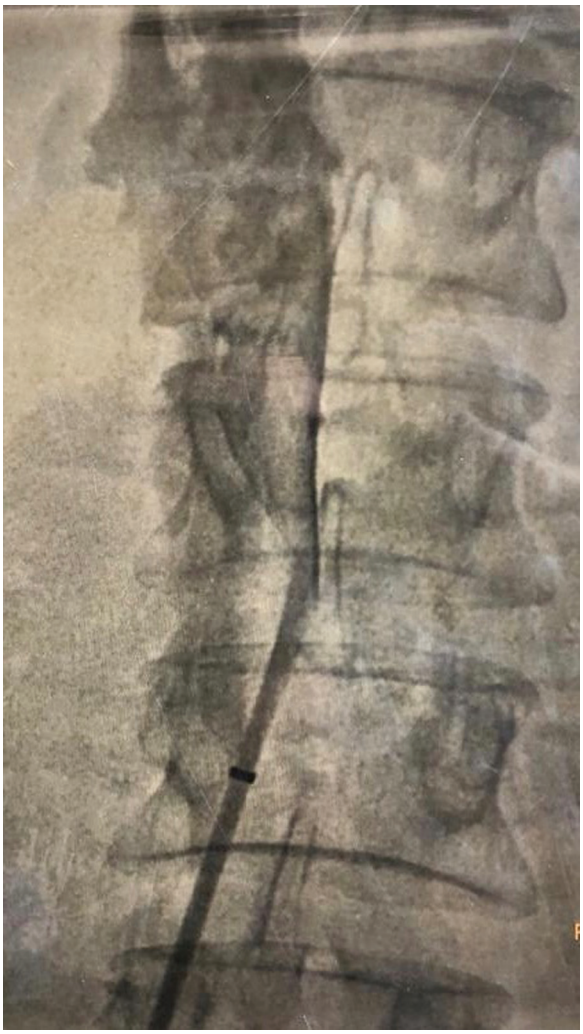
Aspirex catheter inside the inferior vena cava passing the whole length of the thrombus with inferior vena cava filter as protection.

Regarding safety outcomes, all complications occurred due to thrombolysis were observed and managed.

Figure 7

Contrast venogram showing patent inferior vena cava inferior vena cava .

Figure 8



Contrast venogram showing start of lysis process.

Bleeding complications were categorized as major if they led to a hemoglobin decrease of at least 2 g/dl and required transfusion of at least 2 units of packed red blood cells. All other hemorrhages were categorized as minor [15].

The study end points were assessed through a standardized clinical examination and DUS study at preestablished times (i.e. baseline, 6 months, 12 months, and 24 months).

Color-coded DUS was used to assess the patency of the iliofemoral venous segment, defined as complete lysis of all detachable thrombus in the iliofemoral venous segment with spontaneous orthograde venous flow, and to evaluate venous flow variation with respiration.

The primary patency rate was defined as the percentage of patients with successful recanalization and without rethrombosis or required reintervention to maintain patency.

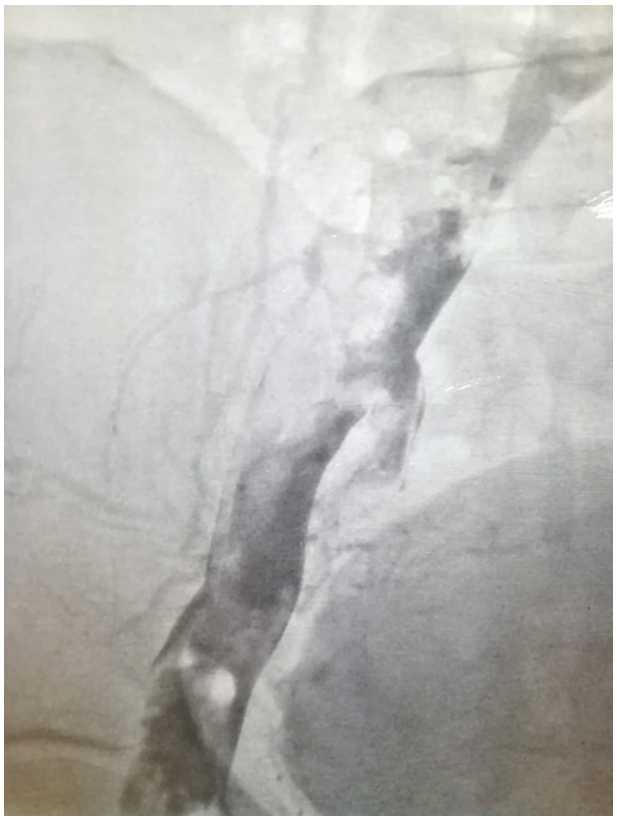
The Villalta score (Table 2) [16] was used for assessment of the presence and severity of PTS, for each item, a score of 0 (none) to three (severe) points was given and points were summed into a total score (range: 0–33). Absence of PTS was defined by a total score of less than five points. PTS was classified as mild (total score 5–9points), moderate (10–14 points), or severe (≥15 points).

Also, the presence and severity of chronic venous disease was assessed using the revised Venous Clinical Severity Score (rVCSS).

Disease-specific QOL was assessed using the English version of the Chronic Venous Insufficiency Questionnaire (CIVIQ-20) after being translated to Arabic, evaluating four domains (physical, psychological, social, and pain) with a total of 20 questions (scored with 1–5 points), with a recall period of the previous week. Total CIVIQ-20 scores range from 20 (excellent QOL) to 100 points (terrible QOL).

Primary end points were iliofemoral venous patency at 12 months, complications rate and patient satisfaction and QOL (CIVIQ-20).

Figure 9



Contrast venogram showing start of recanalization (not completely).

Table 1 Grades of thrombolysis

Grades	Percentage of lysis
Grade I	<50% clot lysis
Grade II	50–90% clot lysis
Grade III	100% with no residual thrombus

Table 2 Villalta score for assessment of post-thrombotic syndrome

Symptoms	Signs
Heaviness	Pretibial edema
Pain	Induration of the skin
Cramps	Hyperpigmentation
Pruritis	New venous ectasia
Paresthesia	Redness
	Pain on calf compression

Secondary end points were recurrence and the occurrence of PTS (Villalta score and rVCSS) within 24 months.

All the study procedures were approved by the IRB (Institutional Review Board) Ethics Committee at Faculty of Medicine, Zagazig University. A written informed consent was voluntarily sought from the participants, after clarifying the aim of the study, methods, and duration of the study. Confidentiality of data was ensured and data was only be accessed by the researchers. Study participants had the right to withdraw from the study at any time without giving reasons and without negatively affecting their medical care.

Table 3 Demographic characteristics of the studied groups

Characteristics	Total (*n*=50)	CDT group (*n*=25)	PCDT group (*n*=25)	*P* value
Age (years)				
Mean±SD	39.44 ±10.8	41.1±10.2	37.7±9.8	0.24
Range	19–56	24–56	19–54	
BMI (kg/m^2)				
Mean±SD	24.8 ±2.31	25.04±2.28	24.68±2.37	0.58
Range	19–30	21–30	19–28	
Sex [*n* (%)]				
Male	22 (44)	10 (40)	12 (48)	0.57
Female	28 (56)	15 (60)	13 (52)	

CDT, catheter directed thrombolysis; PCDT, pharmacomechanical catheter-directed thrombolysis.

Statistical analysis

The collected data were coded, entered, presented, and analyzed by a computer using a data base software program, Statistical Package for the Social Sciences (version 20; SPSS Inc., Chicago, Illinois, USA). Quantitative variables were expressed as mean±SD while qualitative variables were expressed as number and percentage. For quantitative variables, independent samples *t*-test was used as appropriate for normally distributed data. χ^2 and/or Fisher's exact tests were used to detect the relation between different qualitative variables. The results were considered statistically significant at a significant probability, *P* value less than 0.05*.

Results

As illustrated in Table 3) the mean age of the studied patients was 39.44±10.08 years (range: 19–56 years) and the mean value of BMI was 24.8± 2.31 kg/m^2 with the 56% being women. The two groups were matched regarding age, BMI, and sex with no statistically significant difference between them.

About 12% of patients were hypertensive. At least one transient or inherited risk factor for venous thrombosis was reported in 39 (78%) patients with the most frequent risk factor being immobilization (20%). Inherited thrombophilia was present in six (12%) patients with four of them having factor V Leiden. The mean duration between the initial symptoms'

Table 4 Baseline clinical characteristics of patients of the studied groups

Characteristics	Total (*n*=50) [*n* (%)]	CDT group (*n*=25) [*n* (%)]	PCDT group (*n*=25) [*n* (%)]	*P* value
Comorbidities				
IHD	3 (6)	2 (8)	1 (4)	0.50
Hypertension	6 (12)	4 (16)	2 (8)	0.38
DM	4 (8)	3 (12)	1 (4)	0.30
Risk factors for DVT				
Idiopathic	11 (22)	4 (16)	7 (28)	0.19
Hormone therapy[a]	4 (8)	3 (12)	1 (4)	0.30
Smoking	9 (18)	5 (20)	4 (16)	0.48
Postpartum status	5 (10)	2 (8)	3 (12)	0.64
Chemotherapy[b]	2 (4)	2 (8)	0	0.24
Immobilization[c]	10 (20)	6 (24)	4 (16)	0.71
Positive family history of VTE	3 (6)	1 (4)	2 (8)	0.50
Thrombophilia[d]	6 (12)	3 (12)	3 (12)	1.000
Factor V Leiden	4 (8)	2 (8)	2 (8)	0.69
Protein C deficiency	1 (2)	1 (4)	0	0.50
Lupus anticoagulant	1 (2)	0	1 (4)	0.50
Duration of symptoms (days)	6.04±2.61 (1–11)	6.68±2.61 (2–11)	5.40±2.51 (1–10)	0.11
Affected leg				
Right	14 (28)	8 (32)	6 (24)	0.53
Left	31 (62)	14 (56)	17 (68)	0.38
Bilateral	5 (10)	3 (12)	2 (8)	0.64
Location and extension of thrombosis				
Isolated iliofemoral DVT	6 (12)	2 (8)	4 (16)	0.38
Isolated iliac thrombosis	1 (2)	0	1 (4)	0.50
Iliac DVT with femoropopliteal extension	31 (62)	18 (72)	13 (52)	0.14
Iliac DVT with caval involvement	7 (14)	3 (12)	4 (16)	0.68
Iliac DVT with calf veins	8 (16)	6 (24)	2 (8)	0.12

χ^2-test or Fisher's exact test whichever appropriate. CDT, catheter directed thrombolysis; DM, diabetes mellitus; DVT, deep vein thrombosis; IHD, ischaemic heart disease; PCDT, pharmacomechanical catheter-directed thrombolysis; VTE, venous thromboembolism. [a]Oral contraceptive pill, hormonal replacement therapy, or tamoxifen use in breast cancer. [b]Received after radical surgery (one after modified radical mastectomy and the other after radical hysterectomy). [c]Defined as bedridden for greater than 72 h including orthopedic trauma and recent surgery. [d]Defined as documented biochemical hypercoagulable disorders.

Table 5 Immediate outcomes of catheter-directed thrombolysis and pharmacomechanical catheter-directed thrombolysis

Variables	CDT group (*n*=25) [*n* (%)]	PCDT group (*n*=25) [*n* (%)]	*P* value
Immediate lysis grade			
Grade I (<50% lysis)	5 (20)	3[a] (12)	0.631
Grade II (50–90% lysis)	9 (36)	8 (32)	
Grade III (100% with no residual thrombus)	11 (44)	14 (56)	
Further intervention[b]			
CDT+PTA and stenting	3 (12)	5 (20)	0.568
Duration of thrombolysis (min)[c]	48±7.2 h	24±3.2 min	

CDT, catheter directed thrombolysis; PCDT, pharmacomechanical catheter-directed thrombolysis; PTA, percutaneous transluminal angioplasty. [a]Including two technical failure. [b]PTA and stenting was performed over a site of significant stenosis greater than or equal to 50% not for thrombosis. [c]After exclusion of two cases of primary failure.

beginning and randomization was 6.04±2.61 days (range: 1–11 days). About 62% of patients had left-sided thrombus and the majority (62%) was iliac DVT with femoropopliteal extension (Tables 4 and 5).

PCDT was successful in the great majority of patients and grade III thrombolysis was achieved in 14/25 (56%) patients while in CDT it was 11/25 (44%), grade II thrombolysis in PCDT 8/25 (32%) patients while in CDT 9/25 (36%) patients, and grade I thrombolysis in PCDT 3/25 (12%) patients while in CDT 5/25 (20%) patients. In three patients, we failed to resolve the thrombosed venous segment, including two cases of primary technical failure, the wire could not pass up to the iliocaval segment. The mean duration of thrombolysis was 24±3.2 min (20.7–27.3 min) while in CDT it was 48±7.2 h.

A total of 11 bleeding episodes were reported in relation to the 25 PCDT procedures. One episode

of major retroperitoneal bleeding (4%) was seen in the PCDT group on third day postprocedure termination as a result of inadequate control of heparin dose with marked elevation of PTT and thrombocytopenia (The cause was failure to adjust the dose of heparin as during the procedure we put heparinized saline mixture with the dye and force it inside the catheter to delineate the vein.). Eventually, the patient died 1 day later. Most of the minor bleeding events (n=10) were related to the puncture site and are likely to have been caused by multiple punctures during establishment of popliteal vein access. On the other hand, in the CDT group two patients experienced minor bleeding complications related to anticoagulation (P=0.009) (Table 6).

Patency is defined as complete lysis of all detachable thrombus in the iliofemoral venous segment, in our study at 6 months follow-up, the rate of iliofemoral patency as assessed with DUS in the PCDT group was observed in 62.5% of the patients after 6 months and in 16 (66.7%) patients after 12 months. However, in the CDT group, patency was observed in two (8%) of the patients after 12 months and in seven (28%) after 24 months (P=0.001) (Table 7).

As illustrated in Table 8 at 24 months follow-up period 8/25 patients received CDT presented with PTS compared with 5/24 in the PCDT group (P=0.08). Despite the fairly high frequency of PTS overall, most of the patients of both groups presented with mild to moderate PTS with only three cases of severe PTS in the CDT group. In our study, there was statistically significant difference in PTS as assessed with the validated Villalta scale at 6 months between the two treatment groups (Table 9).

When comparing the VCSS and thrombus score in our study, there was statistically significant difference between both groups at 6, 12, and 24 months with more improvement in the PCDT group (P<0.0001) although there was no statistically significant difference between both groups at baseline.

As regards femoropopliteal reflux during the 24 months' follow-up, 11 (44%) patients in the CDT group and 18 (72%) patients in the PCDT group suffered femoropopliteal reflux during the follow-up with significant difference (P=0.04).

When comparing CIVIQ-20 scores between the studied groups, there was statistically significant difference between both groups at 6, 12, and 24 months with more improvement in the PCDT group (P<0.05) although there was no statistically significant difference between both groups at baseline (Table 10).

Table 6 Frequency of complications in the two studied groups

Variables	CDT group (n=25) [n (%)]	PCDT group (n=25) [n (%)]	P
Major bleeding			
Retroperitoneal hematoma	0	1 (4)	0.50
Minor bleeding	2	10	*0.009*
Puncture site bleeding	0	8 (32)	
Skin ecchymosis	1 (4)	2 (8)	
Vaginal bleeding	1 (4)	0	
Pulmonary embolism	0	0	
Death	0	1 (4)	0.50 +

Fisher's exact test. CDT, catheter directed thrombolysis; PCDT, pharmacomechanical catheter-directed thrombolysis.

Table 7 Patency of iliofemoral venous segment as assessed with duplex ultrasonography after 6, 12, and 24 months of treatment among the two studied groups

Items	Total (n=49) [n (%)]	CDT group (n=25) [n (%)]	PCDT group (n=24) [n (%)]	P
Complete lysis (iliofemoral patency)				
6 months	15 (30.6)	0	15 (62.5)	*<0.001**
12 months	18 (36.7)	2 (8)	16 (66.7)	*<0.001***
24 months	25 (51)	7 (28)	18 (75)	*0.001*
Incomplete lysis (recanalization)				
6 months	20 (40.8)	13 (52)	7 (29.2)	0.104
12 months	26 (53.1)	18 (72)	8 (33.3)	*0.015**
24 months	19 (38.8)	14 (56)	5 (20.8)	*0.012**
No lysis (no flow)				
6 months	14 (28.6)	12 (48)	2 (8.3)[#]	*0.002**
12 months	5 (10.2)	5 (20)	0	*0.021**
24 months	5 (10.2)	4 (16)[‡]	1 (4.2)[+]	0.171

χ^2-test or Fisher exact test which appropriate. CDT, catheter directed thrombolysis; PCDT, pharmacomechanical catheter-directed thrombolysis. [¶]One postoperative death (2%). [#]One case of two primary failures; the other due to recurrence at 1 month after primary success. [+]Recurrent case. [‡]One recurrent case at 6 months.

Table 8 Comparing post-thrombotic syndrome at different intervals among the two studied groups

PTS	CDT group (*n*=25) [*n* (%)]	PCDT group (*n*=24) [*n* (%)]	*P*
PTS at 12 months			
No PTS (score 0–4)	17 (68)	21 (87.5)	0.52
Mild (score 5–9)	5 (20)	2 (8.2)	
Moderate (score 10–14)	2 (8)	1 (4.3)	
Severe (score ≥15)	1 (4)	0	
PTS at 24 months			
No PTS (score 0–4)	11 (44)	19 (79.1)	0.149
Mild (score 5–9)	4 (28)	4 (16.6)	
Moderate (score 10–14)	3 (16)	1 (4.3)	
Sever (score ≥15)	1 (12)	0	

CDT, catheter directed thrombolysis; PCDT, pharmacomechanical catheter-directed thrombolysis; PTS, post-thrombotic syndrome.

Table 9 Comparing Villalta scale, thrombus score, and Venous Clinical Severity Score at different intervals among the two studied groups

Variables	CDT group (*n*=25)	PCDT group (*n*=24)	*P*
Villalta scale			
At 12 months	5.32±4.02	3.48±1.4	0.03*
At 24 months	5.56±2.5	4.08±1.1	0.08
Thrombus score			
At baseline	51.48±10.6	53.04±10.14	0.94
At 6 months	29.92±7.3	24.84±4.2	<0.001**
At 12 months	30.08±8.5	25.48±5.53	<0.001**
At 24 months	30.20±8.41	25.80±4.16	<0.001**
VCSS			
Baseline	6.16±0.93	6.1±0.89	0.65
At 6 months	2.92±0.86	1.95±0.80	<0.001**
At 12 months	3.04±0.67	2.04±0.62	<0.001**
At 24 months	3.12±0.83	2.17±0.070	<0.001**

CDT, catheter directed thrombolysis; PCDT, pharmacomechanical catheter-directed thrombolysis; VCSS, Venous Clinical Severity Score. Independent sample *t*-test.

Discussion

PCDT is an effective and safe procedure in the management of DVT with accepted results such as safety and patency rate [17]. CDT is also a good method because it can effectively achieve the patency of the lumen and remove the thrombus lining the venous valves [12].

Developing PTS are often associated with severe economic and health-related QOL problems. About one-third of patients do not return to their baseline QOL after DVT. Also, patients with severe PTS have a functional capacity and QOL metrics similar to those used for cancer or congestive heart failure [16].

Table 10 Comparing Chronic Venous Insufficiency Questionnaire-20 at different intervals among the two studied groups

Variables	CDT group (*n*=25)	PCDT group (*n*=24)	*P*
CIVIQ-20			
CIVIQ: at baseline	51.48±10.6	53.04±10.14	0.59
CIVIQ: at 6 months	29.92±7.3	24.84±4.2	0.005*
CIVIQ: at 12 months	30.08±8.5	25.48±5.53	0.016*
CIVIQ: at 24 months	30.20±8.41	25.80±4.16	0.036*

Independent sample *t* test. CDT, catheter directed thrombolysis; CIVIQ, Chronic Venous Insufficiency Questionnaire; PCDT, pharmacomechanical catheter-directed thrombolysis.

This study is a prospective clinical study that was conducted on 50 patients, who were divided into two groups. The two groups were matched regarding age, BMI, and sex with no statistically significant difference between them. At least one transient or inherited risk factor for venous thrombosis was reported in 39 (78%) patients with the most frequent risk factor being immobilization (20%). Inherited thrombophilia was present in six (12%) patients with four of them having factor V Leiden. About 62% of patients had left-sided thrombus and the majority (62%) was with femoropopliteal extension.

PCDT was successful in the great majority of patients and grade III thrombolysis was achieved in 14/25 (56%) patients, grade II thrombolysis in 8/25 (32%) patients, and grade I thrombolysis in 3/25 (12%) patients. Significant recanalization (grade II or III thrombolysis) was achieved in 22/25 (88%) patients. In three patients, we could not resolve the thrombosed venous segment including two cases of primary technical failure, the wire could not pass up to the iliocaval segment. The mean duration of thrombolysis was 24±3.2 min percutaneous transluminal angioplasty (PTA) and stenting was performed over a site of significant stenosis greater than or equal to 50% not for thrombosis in three patients. The study of Enden *et al*. [12] reported a grade III thrombolysis in 24 (48%) patients, grade II in 20 (40%) patients, and grade I in six (12%) patients who presented within 21 days of DVT and were treated with CDT.

The study of Ye *et al.* [17] included a total of 54 patients with inferior vena cava thrombosis who were treated by PCDT. This study showed a high success rate of PCDT. All patients showed symptom relief after PCDT treatment. Thrombosis recurrence rate within 30 days was 20% (11/54), resulting in a clinical success rate of 80% (43/54).

Regarding the present study, a total of 11 bleeding episodes were reported in relation to the 25 PCDT procedures. One episode of major retroperitoneal bleeding (4%) was seen in the PCDT group on the third day of postprocedure termination. Eventually, the patient died 1 day later. Most of the minor bleeding events (n=10) were related to the puncture site and are likely to have been caused by multiple punctures during establishment of popliteal vein access. On the other hand, two in the 25 CDT procedure patients experienced minor bleeding (P=0.009).

In the study of Ye *et al.* [17], one patient had symptomatic pulmonary embolism and was treated with CDT. Also, one attack of major bleeding had occurred at the femoral vein access site that required blood transfusion. Moreover, seven minor bleeding had been reported, including five cases of bleeding in the access sites and two cases of bleeding in subcutaneous hemorrhages, all of which required no specific treatment.

Patency is defined as complete lysis of all detachable thrombus in the iliofemoral venous segment. In our study at 24 months follow-up, the rate of iliofemoral patency as assessed with DUS in the PCDT group was observed in 62.5% of the patients after 6 months and in 16 (66.7%) patients after 12 months. The higher rate of lysis at 12 months than one at 6 months indicates the ongoing recanalization process. However, in the CDT group, patency was observed in only 8% of patients after 12 months and in seven (28%) after 24 months (P=0.001).

The study of Ye *et al.* [17] estimated rates of primary and secondary patency and they were 76% and 92% at 1 year, respectively, and 63 and 81% at 3 years, respectively. Reocclusion of the treated venous segments occurred in 18 patients.

This was in concordance with Srinivas *et al.* [18] and the TORPEDO trial [19], which reported a patency rate of (80% in CDT: 23% in control; P<0.01) and (64.0% in CDT: 35.8% in control; P=0.004), respectively.

At 24 months follow-up period, 8/25 patients who received CDT presented with PTS compared with 5/24 in the PCDT group. Despite the fairly high frequency of PTS overall, most of the patients of both groups presented with mild to moderate PTS with only three cases of severe PTS in the CDT group. In our study, there was statistically significant difference in PTS as assessed with the validated Villalta scale at 24 months between the two treatment groups with better improvement in the PCDT group.

Ye *et al.* [17]) reported that after a mean follow-up of 26 months, seven patients (7/54; 13%) developed PTS, two patients were mild and five patients were moderate. However, there were no patients with severe PTS in this study during the follow-up. The estimated incidences of PTS were 4 and 25% at 1 and 3 years, respectively.The CaVenT trial [20], which was the first RCT with long-term follow-up for evaluation of additional CDT, proved the benefits of CDT in the prevention of PTS, but still demonstrated a relatively high PTS rate of 41.1 vs 55.6% with standard treatment at 2 years (P=0.047).

Severe PTS occurred in only one patient. In the same study after 5 years of follow-up, 42.5% allocated CDT developed PTS vs 60.6% (P<0.0001) with severe PTS occurred in only five patients, four of them in the CDT group. In the study of Vedantham *et al.* [21], PTS developed over the 24-month period in 47% of patients in the thrombolysis group, 18% were with severe PTS and in 48% of patients in the control group, 24% were severe (P=0.56). Even the incidence of PTS at intermediate follow-up of 12 months in this study was nonsignificant (34% in both groups).

Regarding VCSS and thrombus score in our study, there was statistically significant difference between both groups at 6, 12, and 24 months with more improvement in the PCDT group (P<0.001) although there was no statistically significant difference between both groups at baseline.

Concerning the HRQOL assessment, when comparing CIVIQ-20 scores between the studied groups, there was statistically significant difference between both groups at 6, 12, and 24 months with better quality in PCDT group (P<0.05) after intervention although there was no statistically significant difference between both groups at baseline.

The study of Zhang *et al.* [22] evaluated HRQOL using CIVIQ-2 questionnaire and showed no significant difference between the two groups (20.2 ±14.4 in control vs 16.6±11.0 in CDT; P>0.05), but it

was lower in the CDT group than standard conservative group and this means that CDT was not associated with good QOL after intervention.

Conclusion

PCDT is an effective treatment for lower extremity DVT, and the clinical results achieved were good. PCDT increased patency of iliofemoral vein at 24 months from 28 to 75%, and reduced the absolute risk of PTS development compared with CDT alone. In addition, the mid-term HRQOL was highly better in PCDT.

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Conflicts of interest

There are no conflicts of interest.

References

1 Lee CH, Cheng CL, Lin LJ, Tsai LM, Yang YH. Epidemiology and predictors of short-term mortality in symptomatic venous thromboembolism. Circ J 2011; 75:1998–2004.

2 Kahn SR, Comerota AJ, Cushman M, Evans NS, Ginsberg JS, Goldenberg NA, *et al.* The postthrombotic syndrome: evidencebasedprevention, diagnosis, and treatment strategies: ascientific statement from the American Heart Association. Circulation 2014; 130:1636e61.

3 Lu Y, Chen L, Chen J, Tang T. Catheter-directed thrombolysis versus standard anticoagulation for acute lower extremity deep vein thrombosis: a meta-analysis of clinical trials. Clin Appl Thrombo Hemost 2018; 24:1134–1143.

4 Amin VB, Lookstein RA. Catheter-directed interventions for acute iliocaval deep vein thrombosis. Tech Vasc Interv Radiol 2014; 17:96–102.

5 Guanella R, Ducruet T, Johri M, Miron MJ, Roussin A, Desmarais S, *et al.* Economic burden and costdeterminants of deep vein thrombosis during 2 years followingdiagnosis: a prospective evaluation. J Thromb Haemost 2011; 9:2397–2405.

6 Watson L, Broderick C, Armon MP. Thrombolysis for acute deepvein thrombosis. Cochrane Database Syst Rev 2014; 1:CD002783.

7 Zhang ZH, Shan Z, Wang WJ, Li XX, Wang SM. Outcome comparisonsof anticoagulation, systematic thrombolysis andcatheter-directed thrombolysis in the treatment of lower extremityacute deep venous thrombosis. Zhonghua Yi Xue Za Zhi 2013; 93:2271–2274.

8 Lee CY, Lai ST, Shih CC. Short-term results of catheter directed intrathrombus thrombolysis versus anticoagulation inacute proximal deep vein thrombosis. J Chin Med Assoc 2013; 76:265–270.

9 Vedantham S, Sista AK, Klein SJ. Society of Interventional Radiology and Cardiovascular and Interventional Radiological Society of Europe Standards of Practice Committees. Quality improvement guidelines for the treatment of lower-extremity deep vein thrombosis with use of endovascular thrombusremoval. J Vasc Interv Radiol 2014; 25:1317–1325.

10 Jaff MR, McMurtry MS, Archer SL. American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011; 123:1788–1830.

11 Kuo TT, Huang CY, Hsu CP. Catheter-directed thrombolysis and pharmacomechanical thrombectomy improve midterm outcome in acute iliofemoral deep vein thrombosis. J Chin Med Assoc 2017; 80:72–79.

12 Enden T, Kløw N-E, Sandvik L. Catheter-directed thrombolysis vs. anticoagulant therapy alone in deep vein thrombosis: results of an open randomized, controlled trial reporting on short-term patency. J Thromb Haemost 2009; 7:1268–1275.

13 Haig Y, Enden T, Slagsvold CE, Sandvik L, Sandset PM, Klow NE. Determinants of early and long-term efficacy of catheterdirectedthrombolysis in proximal deep vein thrombosis. J Vasc Interv Radiol 2013; 24:17–24.

14 Protack CD, Bakken AM, Patel N, Saad WE, Waldman DL, Davies MG. Long-term outcomes of catheter directed thrombolysis for lower extremity deep venous thrombosis without prophylactic inferior vena cava filter placement. J Vasc Surg 2007; 45:992–997.

15 Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3:692–694.

16 Vaidyanathan S, Menon RR, Jacob P, John B. Chronic venous disorders: classification, severity assessment, and nomenclature. In: Chronic Venous Disorders of the Lower Limbs: A surgical Approach. 1st ed. Chapter 4, New Delhi, India: Springer 2015. 25–32.

17 Ye K, Qin J, Yin M, Liu X, Lu X. Outcomes of pharmacomechanical catheter-directed thrombolysis for acute and subacute inferior vena cava thrombosis: a retrospective evaluation in a single institution. Eur J Vasc Endovasc Surg 2017; 54:504e512.

18 Srinivas BC, Patra S, Nagesh CM, Reddy B, Manjunath CN. Catheter-directed thrombolysis along with mechanical thromboaspiration versus anticoagulation alone in the management of lower limb deep venous thrombosis – a comparative study. Int J Angiol 2014; 23:247–254.

19 Sharifi M, Mehdipour M, Bay C, Smith G, Sharifi J. Endovenous therapy for deep venous thrombosis: the TORPEDO trial. Catheter Cardiovas Interv 2010; 76:316–325.

20 Enden T, Haig Y, Kløw NE, Slagsvold CE, Sandvik L, Ghanima W, *et al.* Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. Lancet 2012; 379:31–38.

21 Vedantham S, Goldhaber SZ, Julian JA, Kahn SR, Jaff MR, Cohen DJ, *et al.* Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. NEJM 2017; 377:2240–2252.

22 Zhang ZH, Shan Z, Wang WJ, Li XX, Wang SM. Outcome comparisons of anticoagulation, systemic thrombolysis and catheter-directed thrombolysis in the treatment of lower extremity acute deep venous thrombosis. Natl Med J China 2013; 93:2271–2274.