Pulsatile injections versus continuous infusion in catheter-directed thrombolysis for proximal iliofemoropopliteal deep vein thrombosis

Ahmad R. Naga

Alexandria Vascular Unit, Alexandria University, Alexandria, Egypt

Correspondence to Ahmad R. Naga, MD, 51 Saint Jeeny Street, Lotus Bld, Kafr Abdo, Roushdy, Alexandria, 2354, Egypt.
Tel: +20 120 767 2767/20 127 588 9994; fax: 034875635;
e-mail: ahmadnaga29@gmail.com

Received: 5 February 2021
Revised: 25 February 2021
Accepted: 12 March 2021
Published: 12 October 2021

The Egyptian Journal of Surgery 2021, 40:577–584

Context
The yearly incidence of first attack of symptomatic deep vein thrombosis (DVT) in adults varies from 50 to 100 per 100 000 population. Catheter-directed thrombolysis (CDT) involves the administration of a thrombolytic drug through a numerous side-holes catheter placed straight into the vein. The intrathrombus delivery can be done either as pulsatile injections (PI) or continuous infusion (CI).
Aims
The objective of this study was to compare the delivery of the recombinant tissue-plasminogen activator drug by PIs versus CI in CDT for iliofemoropopliteal DVT in terms of clinical and hemodynamic outcome.
Settings and design
This was a single-center retrospective study done between February 2017 to February 2020. A total of 29 patients were treated by CDT for proximal iliofemoral DVT.
Patients and methods
Patients were randomly divided into two groups: group A had the drug delivered by the PI, and group B had it delivered by CI.
Statistical analysis
used Statistical Package for the Social Sciences (SPSS) 15.0 was used. Values were compared with a paired sample *t* test. *P* values less than 0.05 were considered significant.
Results
It had clearly showed that PI patients had better results regarding grade of thrombus lysis as well as duplex scan assessment of lumen narrowing, collateralization, and reflux. Moreover, PI patients had statistically better scores regarding Charing Cross Venous Ulceration Questionnaire, Venous Segmental Disease Score, Venous Clinical Severity Score, Villalta score, and 36-Item Short Form Health Survey for quality of life.
Conclusions
CDT delivered by the PI technique is safe and effective in treating proximal leg DVT when compared with the CI technique.

Keywords:
catheter-directed thrombolysis, proximal iliofemoropopliteal deep vein thrombosis, venous thromboembolism

Egyptian J Surgery 40:577–584

1110-1121

Introduction

The yearly incidence of first attack of symptomatic deep vein thrombosis (DVT) in adults varies from 50 to 100 per 100 000 population [1,2]. Iliofemoral DVT commonly affects the left leg, secondary to May–Thurner syndrome [3]. The incidence of postthrombotic syndrome following iliofemoral DVT ranges from 24 to 45%, with the devastating accompanying symptoms and affection of quality of life [4].

Catheter-directed thrombolysis (CDT) involves the administration of a thrombolytic drug through a numerous side-holes catheter placed straight into the vein. The intrathrombus delivery can be done either as pulsatile injections (PI) or continuous infusion (CI); the former has been shown to achieve better results in a single nonrandomized observational cohort study [5]. The most common drug used is the recombinant tissue-plasminogen activator (rt-PA), the volume of which varies from 20 to 120 ml; generally, rt-PA should not exceed 1 mg/h [6].

The objective of this study was to compare the delivery of the rt-PA drug by PIs versus CI in CDT for

iliofemoral DVT in terms of clinical and hemodynamic outcome.

Patients and methods

This was a single-center retrospective study done between February 2017 and February 2020. A total of 29 patients were treated by CDT for proximal iliofemoral DVT during that period. Patients included were ambulatory cases aged between 18 and 65 years old, first attack of acute proximal iliofemoral DVT documented by color duplex ultrasound (CDU), within less than 14 days, and life expectancy more than 1 year. Exclusion criteria were patients with ASA more than or equal to 4, recurrent DVT, and those presenting beyond 2 weeks of symptoms. Any patient with a contraindication to thrombolysis was also excluded; these included active internal hemorrhage, stroke within previous 2 months, recent gastrointestinal bleeding, severe hypertension (>180/100), postpartum within the past 20 days, thrombocytopenia (platelets<100/dl), recent surgery less than 14 days, liver failure, end-stage renal failure, coagulopathy, and psychological illness that may interfere with compliance of admission.

Upon admission, all patients had thorough clinical examination and routine laboratory tests. Clinical examination entailed measuring the thigh circumference at a mid-point between anterior superior iliac spine and knee joint level in centimeter. A urine catheter was inserted very cautiously by a senior doctor to avoid any urethral injury. In the angiosuite under aseptic technique, patients were allowed to lie prone, and ultrasound-guided insertion of a 5-F sheath into the ipsilateral popliteal vein was secured. Then, contrast material was injected through the sheath to detect the thrombus distal extent. Infusion catheter (fountain infusion systems; Merit Medical Systems Inc., South Jordan, Utah, USA) with multiple side holes was placed into the thrombus with tip occlusion beyond the upper extent of the thrombus. Initially, prophylactic dexamethasone 4 mg and pheniramine maleate (Avil) 10 mg were injected intravenously to guard against anaphylactic shock. Standard unfractionated heparin infusion of 100 U/h was started into the sheath through a syringe pump. After preparation of the rt-PA (Alteplase; Boehringer Mannheim, Mannheim, Germany) vial, a bolus dose of 5 mg of the drug was injected into the catheter over 30 min by a separate syringe pump. The sheath was then kept in place using 2/0 silk suture into the skin, then covered by dressing. If there were no adverse effects after 30 min, then the procedure would proceed as follows. Patients either received the drug by the PI technique or by CI. For those who had the PI method, a 20-ml syringe from the drug was plugged into the pistol, which was then calibrated to give 5–7.5 ml per shot according to the preferred dosage; the routine dose was one pistol shot every half an hour. However, the other group of patients (CI) received the drug in a continuous intravenous manner at a rate of 1 mg/h. Whatever the technique followed, this protocol was continued for 12–72 h according to the total dose and results. All patients were kept in ICU to monitor vital signs and laboratory results; fibrinogen levels were maintained above 100 mg/dl and aPTT levels between 50 and 70 s. Every 24 h, the success of lysis was graded by venography by the single principal investigator using a scale based on the percentage of thrombolysis accomplished [7]. Grades of lysis are shown in Table 1. The procedure was terminated once no more thrombus was visualized or when no more progress is detected between two successive venographies. The duration of the procedures was calculated in hours, and patients were divided into three groups: less than or equal to 24 h, 24–48 h, and 49–72 h. Upon completion, the sheath was removed 6 h after termination of the thrombolytic drug. Patients were transferred to the ward and started on new oral anticoagulants for at least a year along with above-knee class II graduated elastic hosiery (23–32 mmHg). After 48 h of the procedure, all patients had a CDU to verify patency of venous segment treated.

The study design entailed dividing the patients into two groups: group A received the drug by the PI technique, and group B had it delivered by CI. Patients were recalled for follow-up at 6 and 24 months for clinical examination, CDU scan, assessment of venous insufficiency using different scoring systems, and quality of life. Measurement of thigh circumference was repeated on every visit. CDU assessment entailed three main parameters: lumen narrowing in comparison with the contralateral side, presence of collateralizations, and valve dysfunction (Table 2) [8,9]. This was performed in a vascular laboratory by a single experienced vascular ultrasonographer, in a temperature-controlled environment (21±1°C), using the Accuson Sequoia 512 (Siemens AG, Medical

Table 1 Grades of lysis achieved

Grade I	<50% lysis
Grade II	50–99% lysis
Grade III	100% with no residual clot

Solutions, Zurich, Switzerland), fitted with an 8-MHz linear array transducer.

The venous scoring systems used were the Charing Cross Venous Ulceration Questionnaire [10], the Venous Segmental Disease Score, and the Venous Clinical Severity Score, derived from the Venous Disability Score [11] and the Villalta score [12]. The 36-Item Short Form Health Survey [13] was used to assess the quality of life.

Informed consent has been taken from all patients after explaining to them the nature and benefit of the study. All calculations were performed with the Statistical Package for Social Sciences (SPSS), 15.0 (Statistical analysis was done using IBM SPSS statistics for windows, Version 23.0. Armonk, NY: IBM Corp). Values of the injured and healthy sides were compared with a paired sample *t* test. *P* values less than 0.05 were considered significant. This study was approved by the Institutional Review Board of the University of Alexandria.

Results

A total of 29 cases of proximal leg DVT have been done at the unit during the past 3 years. Upon recall of patients, five cases could not be traced for follow-up. Two cases had incomplete procedures and were not included in data analysis. Case #3 had family history of thrombophilia and presented with iliofemoropopliteal DVT. Initially, he showed grade II lysis at the iliofemoral segment after 24 h. However, on the second venography, he had acute rethrombosis of the whole axis; thus, the procedure was terminated. Another patient, case #9, had presented with bilateral extensive iliofemoral DVT with distal inferior vena cava (IVC) thrombosis. Two catheters were inserted up to the IVC and the routine rt-PA dose was divided upon both of them; unfortunately, after 36 h, no lysis was observed at all. The patient was very irritable and experienced cardiac arrhythmias; therefore, the treatment was withdrawn. Therefore, the study analyzed the data for 22 cases, divided into two groups: group A had PI (n=13) and group B CI (n=9).

Table 3 shows the patients' demographic data. Most of the treated legs were on the left side: 69% in PI group and 56% in CI group. More than half of the cases in both groups had idiopathic DVT. None of the cases received the treatment more than 11 days after symptoms, with a mean±SD of 4.63±3.18 in PI group versus 3.92±2.56 in CI group. Two cases that had concomitant pulmonary embolism on presentation had an IVC filter inserted before the procedure.

The mean duration of the procedures was 44.54 ±9.03 h. Table 4 demonstrates the distribution of patients according to the time spent for the whole procedure.

Regarding the degree of lysis toward the end of the procedure (Table 5), only one patient from group CI had no lysis at all; nevertheless, there was a statistically significant difference between the two groups (P=0.009), with far less thrombus observed in patients receiving the drug by the pulsatile spray technique (PI). After 48 h of the end of the procedure, CDU revealed all treated segments to be patent. Color duplex scan results done at 6 and 24

Table 2 Criteria for color Duplex ultrasound assessment

Vein lumen	Normal	Reduction ≤25%	Reduction 25–50%	Reduction >51%
Collateralization	Absent	Mild	Moderate	Severe
Valve dysfunction	Normal	Mild	Moderate	Severe

Table 3 Patients' demography and clinical data

	Group A 'PI' (N=13)	Group B 'CI' (N=9)
Age	45.08±11.96	39.56±10.08
Sex [n (%)]		
Female	6 (46)	7 (78)
Male	7 (54)	2 (22)
Side [n (%)]		
Left	9 (69)	5 (56)
Right	4 (31)	4 (44)
Comorbidity [n (%)]		
Hormonal therapy	1 (8)	2 (22)
Idiopathic	7 (54)	5 (56)
Immobilization	2 (15)	2 (22)
Postpartum 21 days	1 (8)	0
Thrombophilia	2 (15)	0
Extent [n (%)]		
Iliac	4 (31)	3 (33)
Iliofemoral	6 (46)	4 (45)
Iliofemoropopliteal	3 (23)	2 (22)
Duration of symptoms (days)	4.63±3.18	3.92±2.56

CI, continuous infusion; PI, pulsatile injection.

Table 4 Distribution of patients according to duration of the procedure

Duration of the procedure	Group A 'PI' (N=13) [n (%)]	Group B 'CI' (N=9) [n (%)]
≤24 h	1 (8)	0
24–48 h	8 (61)	3 (33)
49–72 h	4 (31)	6 (67)

CI, continuous infusion; PI, pulsatile injection.

Table 5 Comparison between the two studied groups regarding clinical lysis

Clinical lysis	Group A 'PI' (*N*=13) [*n* (%)]	Group B 'CI' (*N*=10) [*n* (%)]	*P* value
No lysis	0	1 (10)	0.009
I	2 (15)	7 (70)	
II	6 (46)	2 (20)	
III	5 (39)	0	

CI, continuous infusion; PI, pulsatile injection.

Table 6 Comparison between the two studied groups regarding color duplex ultrasound at follow-up

Color duplex ultrasound criteria	Group A 'PI' (*N*=13) [*n* (%)]	Group B 'CI' (*N*=9) [*n* (%)]	*P* value
Lumen 6 m			
Normal	7 (54)	0	0.001
<25%	5 (39)	0	
25–50%	1 (7)	6 (67)	
>50%	0	3 (33)	
Lumen 24 m			
Normal	9 (69)	0	0.001
<25%	4 (31)	0	
25–50%	0	4 (44)	
>50%	0	5 (56)	
Collaterals 6 m			
Absent	6 (46.2)	0	0.001
Mild	5 (38.5)	0	
Moderate	2 (15.4)	5 (55.6)	
Severe	0	4 (44.4)	
Collaterals 24 m			
Absent	8 (61.5)	0	0.001
Mild	5 (38.5)	0	
Moderate	0	6 (66.7)	
Severe	0	3 (33.3)	
Valve 6 m			
Mild	5 (38.5)	1 (11.1)	0.002
Moderate	1 (7.7)	4 (44.4)	
Normal	7 (53.8)	0	
Severe	0	4 (44.4)	
Valve 24 m			
Mild	3 (23.1)	0	0.001
Moderate	0	6 (66.7)	
Normal	10 (76.9)	0	
Severe	0	3 (33.3)	

CI, continuous infusion; PI, pulsatile injection.

months respectively are shown in Table 6. Statistically significant differences were observed favoring group A (PI).

Clinically, when comparing the thigh circumference (cm) before the procedure and at the follow-up visits, we noted that although there was neither clinical nor statistical significance between the two groups, however, as shown in Table 7, there was a statistically significant difference between measurements at 6 and 24 months among the

Table 7 Comparison between the two studied groups regarding thigh circumference at follow-up

Thigh circumference (cm)	Group A 'PI' (*N*=13)	Group B 'CI' (*N*=9)	*P* value
Preoperative	68.85±9.21	62.67±8.90	–
At 6 m	61.15±9.43	57.67±7.98	0.398
At 24 m (cm)	50.54±8.95	51.78±4.89	0.667
P value	0.036	0.011	

CI, continuous infusion; PI, pulsatile injection.

patients of the same group. Figure 1a–f shows an example of a case with iliofemoropopliteal DVT treated in the study.

Concerning the venous scoring systems and quality of life assessment, all parameters were favoring the PI technique (Table 8).

No major bleeding complications were encountered. However, hematuria and oozing around the sheath were the most common misshapen seen. Table 9 summarizes the complications recorded.

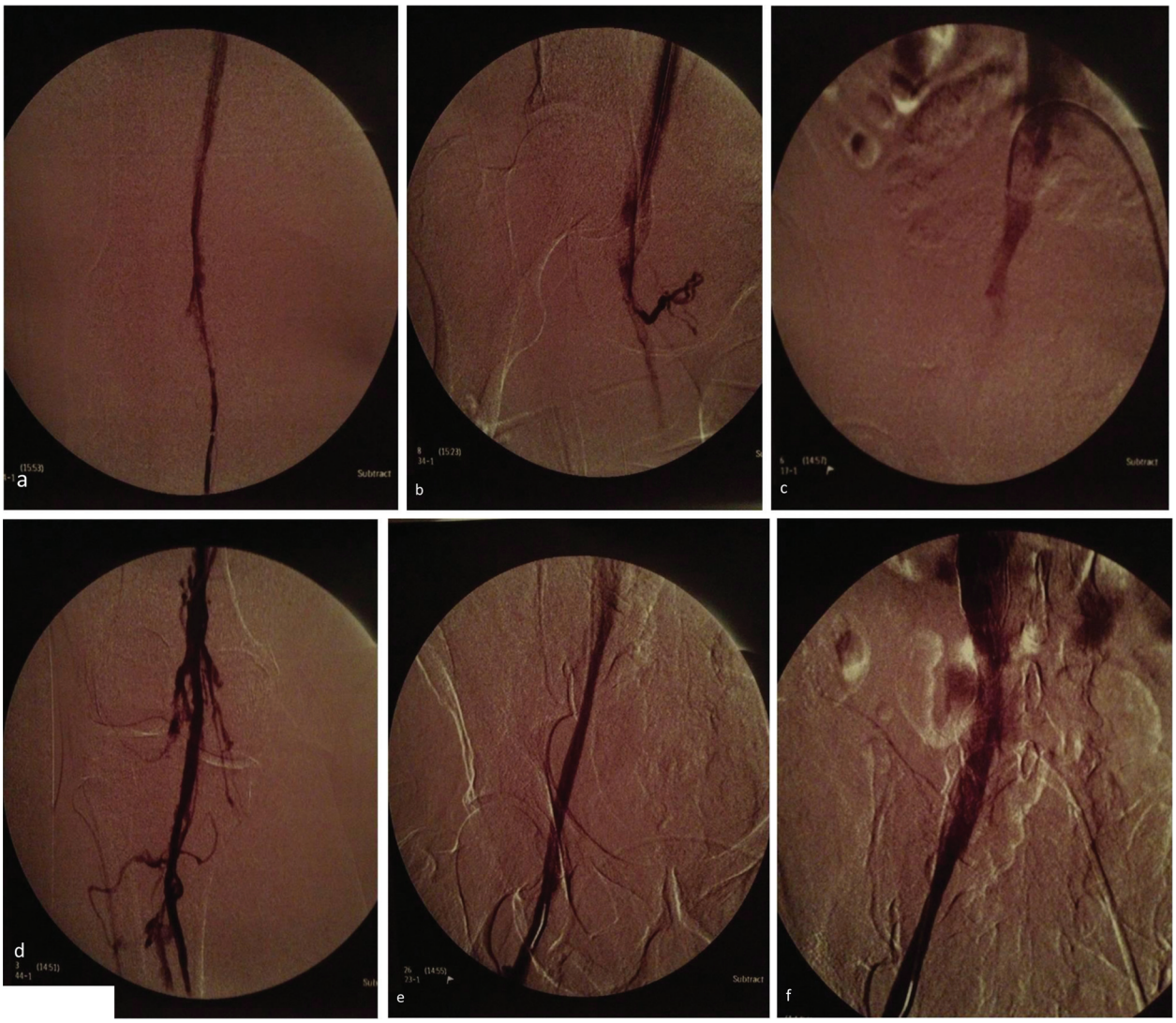
Figure 2a–i shows another example of a case with extensive iliofemoropopliteal DVT treated with CDT.

Discussion

This was a single-center retrospective study that involved 22 patients treated with CDT for acute proximal leg DVT within a 3-year period. The main goal of this study was to demonstrate the difference it makes when delivering the rt-PA drug using PI compared with CI. It clearly showed that PI patients had better results regarding grade of thrombus lysis as well as duplex scan assessment of lumen narrowing, collateralization, and reflux. Moreover, PI patients had statistically better scores regarding Charing Cross Venous Ulceration Questionnaire, Venous Segmental Disease Score, Venous Clinical Severity Score, Villalta score, and 36-Item Short Form Health Survey for quality of life.

Among the early cases, our strategy was using the CI modality to avoid the trouble that the PI might cause. By time, owing to the improved results, the infusion strategy shifted to the PI technique and the ICU staff got more acquainted with it. This is under the assumption that the jet-like pistol shots delivered into the catheters' side-holes result in better 'physical' effect on the thrombus, thereby decreasing the procedure time. There should be a well-trained dedicated ICU nursing staff to clearly follow the dose adjustments and delivery every half an hour over the whole period of treatment, using the pistol syringe.

Figure 1



Before (a) Popliteal vein, (b) Femoral vein, (c) Iliac vein. After (d) Popliteal vein, (e) Femoral vein, (f) Iliac vein.

Table 8 Comparison between the two studied groups regarding venous scoring systems and quality of life at follow up

	Group A 'PI' (*N*=13)	Group B 'CI' (*N*=9)	*P* value
VDS 6 m	0.77±0.73	2.22±0.44	0.001
VDS 24 m	0.77±0.73	2.11±0.78	0.001
VCSS 6 m	7.31±2.90	17.22±3.27	0.001
VCSS 24 m	6.62±2.18	16.11±3.95	0.001
CXVUQ 6 m	64.46±6.44	78.67±4.85	0.001
CXVUQ 24 m	33.62±8.00	65.44±6.62	0.001
Villalta score 6 m	9.62±3.18	19.44±4.07	0.001
Villalta score 24 m	5.46±2.07	12.67±4.39	0.001
QOL 6 m	69.85±6.58	53.00±5.41	0.001
QOL 24 m	87.31±5.15	67.33±5.17	0.001

CI, continuous infusion; CXVUQ, Charing Cross Venous Ulceration Questionnaire; PI, pulsatile injection; QOL, quality of life; VCSS, Venous Clinical Severity Score; VDS, Venous Disability Score.

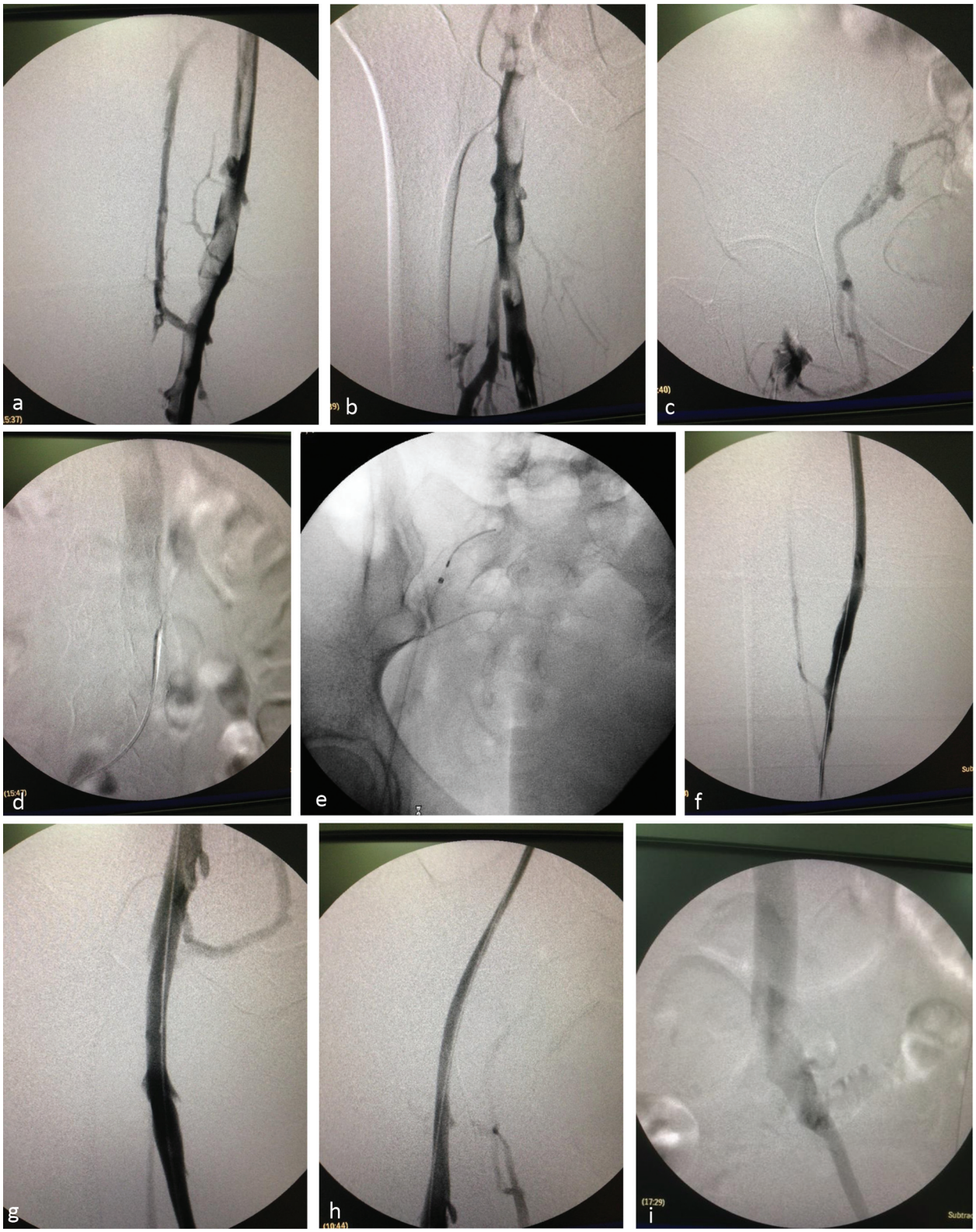
Table 9 Complications

Complications	Group A 'PI' (*N*=13) [*n* (%)]	Group B 'CI'(*N*=9) [*n* (%)]
Hematuria	8 (62)	4 (44)
Vaginal bleeding	5 (38)	2 (22)
Sheath minor bleeding	7 (54)	3 (33)
Hypotension	2 (15)	3 (33)
Arrhythmia	1 (8)	0
Major bleeding	0	0
Drug allergy	0	0
Death	0	0

CI, continuous infusion; PI, pulsatile injection.

Few technical tips have been learned throughout the study. Whether the popliteal vein is thrombosed or not, it makes no difference in the approach; one can still insert the sheath into the engorged blocked vein. Ultrasound-guided approach is vital to avoid

Figure 2



Before (a) Popliteal vein, (b) Femoral vein, (c) Iliac vein, (d) Patent IVC, (e) Tip occluded above thrombus. After (f) Popliteal vein, (g) Femoral vein, (h) Iliac vein, (i) Iliocaval junction.

multiple puncture holes in the popliteal vein that can cause future bleeding, aborting the whole procedure. Although some authors have shown promising results when using the posterior tibial vein approach [14], we find it too difficult and unbeneficial. As per IFU, the rt-PA drug must be kept in the refrigerator at 4–10°C. Lastly, harsh maneuver using a stiff guidewire to manipulate what seems to be a stenosed iliac vein in the first setting is not recommended; this might precipitate retroperitoneal hematoma upon

thrombolysis. Therefore, it is better to wait until some lysis occurs that might facilitate crossing in the next venography session.

Routine prophylactic IVC filter deployment to reduce pulmonary embolism before CDT is not well justified [15,16]. In the present study, two patients had an IVC filter placed before CDT because they already had documented pulmonary embolism by computed tomography pulmonary angiography. The importance of IVC filter could be only defensible if mechanical aspiration thrombectomy devices were used adjunctively [17,18].

The study participants had few complications. Minor subcutaneous hematoma at the popliteal fossa was the commonest and shall never abort the procedure; manual compression is usually enough. Moreover, hematuria was considered a normal incident, and as long as hemoglobin level did not drop by more than 2 g/dl, no blood transfusion is indicated. As mentioned earlier, two patients had failed thrombolysis and were transferred to another hospital for a trail of pharmacomechanical aspiration and thrombolysis. The evidence behind CDT came from the Norwegian CaVenT study [19], published in 2012, the protocol of which had been followed in this study. In 2017, the ATTRACT trail [20] was released which questioned the value of pharmacomechanical CDT in proximal leg DVT. However, it had been criticized for randomization issues and until now CDT is well validated in symptomatic iliofemoral DVT.

Proof on differences in hemodynamic outcome between PIs and CI is not well mentioned. A single randomized trial had demonstrated that PIs were better than CI for the treatment of acute leg ischemia [21]. Nevertheless, our findings are similar to what Foegh *et al*. [5] concluded that the use of the PIs for CDT resulted in better patency including reduced reflux rates on the long term.

The strengths of the current study are the comparative design, the hemodynamic assessment of the deep veins using CDU, and the different venous scoring systems used. This study also has unavoidable limitations. It was a nonrandomized observational study that included highly selected participants. Therefore, choosing the best candidates for CDT cannot be made from this study. Generally, observational studies are predisposed to bias resulting from baffling by indication. For instance, younger patients who are expected to have better results, get a priority for CDT versus conventional anticoagulation.

Conclusion

In conclusion, PIs have shown superiority over CI in the management of iliofemoropopliteal DVT by CDT. Higher grades of thrombus lysis were achieved as well as better results visualized by color duplex in terms of lumen narrowing, collateralization, and reflux. Lastly, PIs showed statistically better scores in all venous scoring systems used in the study.

Acknowledgment

The author thanks Dr Rashad Bishara, Chief of Vascular Surgery, El-Sahel Teaching Hospital, Egypt for his exceptional support in terms of methodology for the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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