Feasibility and safety of percutaneous hydrodynamic thrombolysis techniques in management of acute proximal lower limb deep vein thrombosis

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Introduction
Currently, there are different treatment options of deep vein thrombosis (DVT) available, and all of which have their own associated adverse effects. Pharmacomechanical thrombolysis (PMT) is a minimally invasive catheter-based intervention that uses a retrograde-directed saline jet under pressure to fragment, macerate, or disrupt the occlusive venous thrombus after lacing it with thrombolytic drugs followed by aspiration of the thrombus material.
Patients and methods
This is a prospective study examining the use of PMT in management of unilateral acute lower limb DVT for some cohort of patients with no contraindication to thrombolysis who presented to our vascular surgery units in the period from December 2019 to June 2020.
Results
A total of 25 patients with acute proximal lower limb DVT were selected for PMT, with an average age of 43.2 years (range: 27–53 years). There were 13 (52%) females and 12 (48%) males. PMT was found to be successful in 21 (84%) patients. The procedure time ranged from 28 to 55 min (average 45 min), and in all patients, the access was gained via the ipsilateral popliteal vein. At first month, the patency rate was found to be 84% (21/25) and 76% at the sixth month (19/25).
Conclusion
In selected group of patients with no contraindications to thrombolysis, PMT can be safely used with good results in terms of patency and lower incidence of developing postthrombotic limb symptoms.

Keywords:
deep venous thrombosis, mechanical thrombolysis, pharmaco, thrombolysis

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Introduction

Deep vein thrombosis (DVT) is considered a common lower limb venous problem that may be associated with many cardiovascular and/or local limb complications. Acute complications include life-threatening pulmonary embolism (PE) or phlegmasia cerulea dolens that might end up with limb-threatening venous gangrene. On the contrary, chronic long-lasting complications from DVT may occur and include chronic venous insufficiency and postthrombotic syndrome (PTS), which may affect the patient's overall quality of life [1]. A wide variety of treatment options of DVT are currently available, such as anticoagulation drugs, thrombolysis, and operative venous thrombectomy, with each method having its own associated adverse effects [1]. Abnormally increased ambulatory venous pressures causing a walking venous hypertension has been recorded to occur in up to 80% of patients with history of lower limb DVT, and many cases had ended up with disabling venous claudication [2]. Those patients plagued with chronic venous insufficiency usually are manifested by persistent symptoms of walking venous hypertension, chronic leg/foot edema, and may even present with leg venous ulceration [2]. It was found that near 50% of patients with acute lower limb DVT who were treated with anticoagulation solely will eventually develop long-term leg and foot complications like PTS symptoms [3]. Patients with acute ilio-femoral DVT, in particular, are the group that usually experiences most severe forms of postthrombotic manifestations [4–6]. Furthermore, near 95% of PTS cases will develop worsening venous reflux symptoms by 5 years with chronic limb ulceration affecting ~80% of patients by 10 years [7]. This risk of having a PTS tends to increase progressively over time after lower limb acute deep venous thrombosis to ~30%, with an average range of 16–82% [8–10]. Despite anticoagulation therapy alone remaining the gold standard for acute DVT treatment, still however the idea of preserving the valve functions by early thrombus

removal is felt to reduce the risk of PTS, especially in cases with proximal ilio-femoral vein DVT. Percutaneous catheter-directed endovascular procedures are less invasive, with a fairly shorter recovery time and yet less patient discomfort. There are many different endovascular procedures available for acute lower limb DVT treatment including catheter-directed thrombolysis (CDT), mechanical thrombectomy, and pharmacomechanical thrombolysis (PMT), also postthrombus extraction angioplasty and/or stenting can be added to any of these procedures [3]. PMT is a minimally invasive catheter-based procedure that uses a mechanical device to fragment, macerate, or disrupt the occlusive fresh venous thrombus after lacing it with jets of thrombolytic drugs followed by aspiration of the fragmented thrombus [2]. Preprocedural placement and postprocedural removal of retrievable inferior vena cava (IVC) filters are advocated by many operators to guard against the possible risk of PE [11–15]. This prospective study was aiming primarily to assess the feasibility, effectiveness, and safety of PMT in patients with acute or subacute unilateral provoked or non-provoked proximal lower limb DVT affecting the iliac, common femoral, and/or femoral vein segments.

Patients and methods

Study design

This is a prospective study where percutaneous PMT utilizing a dedicated machine was offered to selected group of patients with acute lower extremity DVT presenting with lower limb symptoms lasting 14 days or less from onset of complaint and affecting the iliac, common femoral, and/or femoral vein segments with no any absolute or relative contraindications for thrombolytic therapy. After obtaining an ethical approval from the local health authorities inside the two hospitals represented by surgery committee & medical board. Patency of the ipsilateral popliteal vein was a standard requirement to help gain an access for the intervention. The study was conducted at the vascular surgery units in Saudi-German Hospital in Dammam and Soliman Fakeeh Hospital in Jeddah; both units are operated by vascular surgery consultants from Cairo University during the period from December 2019 to June 2020. We have selectively included patients with acute or subacute unilateral lower limb ilio-femoral DVT whether provoked or nonprovoked. Patients presented with bilateral lower extremity DVT were not included in the study. In almost all cases, the diagnosis was confirmed by venous duplex ultrasound scanning of the affected limb, which was also used to assess patency of the ipsilateral popliteal vein and to outline the extent of the affected venous segments using the standard techniques of venous wall compressibility, thrombus echogenicity, and augmentation response to distal compression. The preprocedure and postprocedure venous duplex studies were done by a single ultrasound operator to eliminate any subjective individual errors in assessment.

The AngioJet thrombectomy system

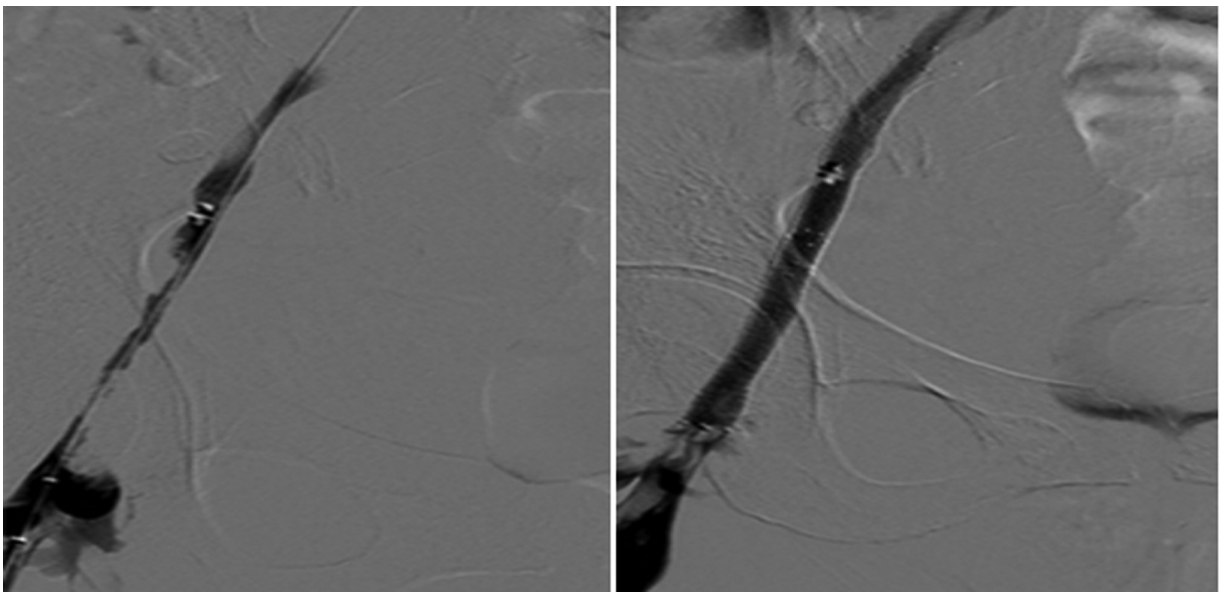
We have used the AngioJet rheolytic thrombectomy system (Boston Scientific Vascular, Watertown, Massachusetts, USA) for the procedure. The system consists of a single-use thrombectomy/aspiration catheter, a single-use pump set, and a pump console (drive unit). The 6-Fr aspiration catheters have a useable working length of 120 cm and are introduced over a standard 0.035-inch guide wire. The catheter configuration consists of one lumen to provide flow of saline at high pressure from an inflow window near the catheter tip and another larger lumen for the guide wire passage and at the same time provide an outflow for the thrombus debris. Once activated, the pump generates pulsatile saline jets at high-pressure flow that exits at the catheter tip forming multiple retrograde-directed jets causing vacuum effect (Venturi Effect). The saline is infused forcibly at high pressure (~10 000 psi) in six high-velocity jets; these jets create a low-pressure zone at the catheter tip that is in balance with the evacuation rate at the catheter side holes generating a vacuum that draws thrombus through the holes between the two radiopaque markers. Once captured by the holes, the thrombus then becomes fragmented by the saline jets and is returned to the console. The catheters have a power pulse delivery feature that allows for infusion of a thrombolytic agent into the thrombus to soften it before mechanical lysis by the saline jets. We have used a thrombolytic solution composed of 200 ml of normal saline combined with 5 mg of recombinant tissue plasminogen activator (rTPA; Alteplase; Altplase^{TM}, Boehringer Ingelheim, Ingelheim am Rhein, Germany). After positioning the catheter within the thrombus over a guide wire, the power pulse mode is used for lacing the thrombus with the thrombolytic solution allowing a dwell time of 15–20 min, and then the catheter is activated in the open position and the hydrodynamic mechanico-lysis/aspiration is started.

The procedure

A written informed consent was obtained from every patient enrolled in the study explaining the nature of the procedure, the expected clinical benefits, possible side effects of thrombolytic drugs, and all anticipated intraoperative or postoperative complications. All procedures were done in the angiography suite under

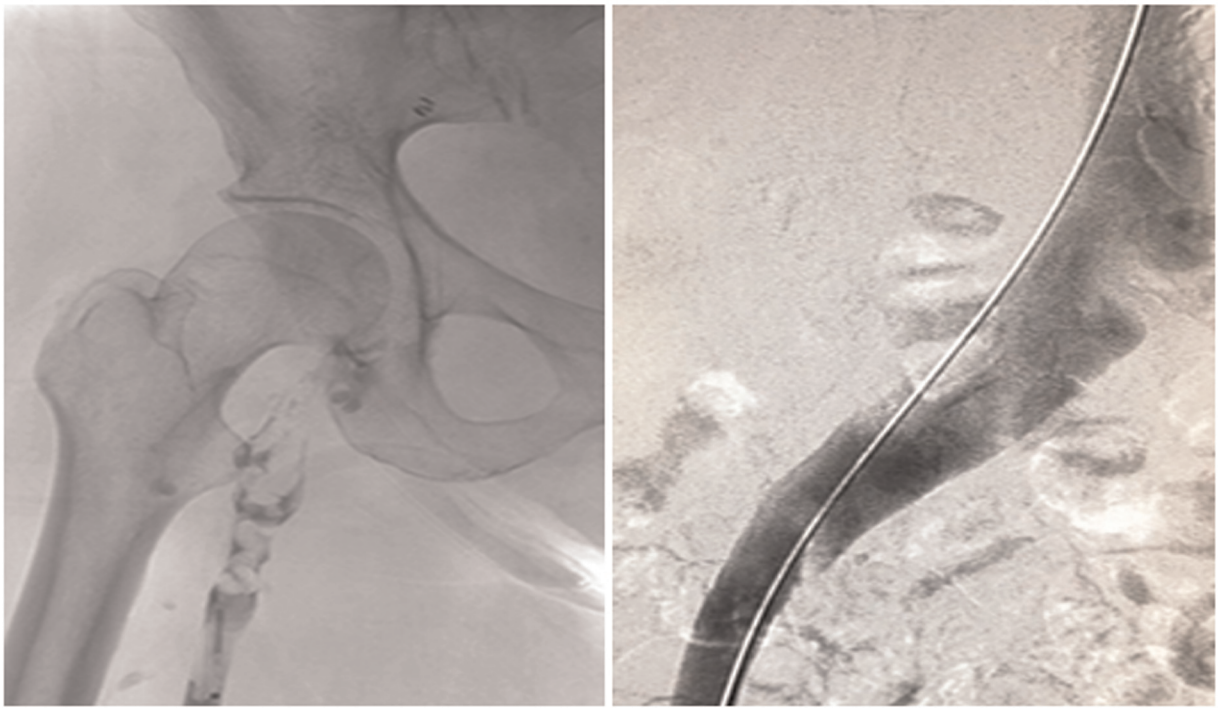
complete cardiovascular and respiratory monitoring with local anesthesia using lidocaine 2%, supplemented by conscious sedation whenever needed. At the beginning of the intervention, the patient was laid in the supine position and a needle puncture through the contralateral common femoral vein was made under ultrasound guidance followed by steering a 0.035-inch guide wire (Glidewire; Terumo Medical, Tokyo, Japan) up to IVC. A suitable retrievable vena cava filter (OPTEASE; Cordis, Miami, Florida, USA) was positioned below the level of renal veins opposite the second and third lumbar vertebrae (L2–L3) on a 6-Fr sheath after obtaining an initial angiogram of IVC and iliac veins to outline the extent of the patent venous segments. After IVC filter placement and manual compression of the venipuncture site, the patient was turned to prone or lateral position, and a 6-Fr introducer sheath (11 cm) was inserted through ipsilateral patent popliteal vein using the ultrasound guidance. A 0.035-inch guide wire was passed through the thrombosed vein segment up till the patent IVC followed by the aspiration thrombectomy catheter. The 6-Fr thrombectomy/aspiration catheter (Solent Omni AngioJet, Boston Scientific Vascular) was accurately positioned proximal to the thrombosed ipsilateral ilio-femoral vein segments. We have used a single mechanical thrombectomy pass through the thrombosed segment followed by infusion of thrombolytic solution and dwell (usually for 15 min) and then continuing with thrombectomy. We usually started catheter activation from femoral vein segment just distal to the occlusive thrombus and going proximally. We tend to limit our activation run to 60 s with 1–2-min breaks to limit the degree of red blood cell disruption that comes in contact with the high-velocity saline jets and vessel wall trauma. The procedure was continued until complete dissolution of the occlusive thrombus, or at least, removal of 90% of the thrombus load was achieved (the company recommends cumulative run times of 4–8 min in a free-flowing blood field and 5–10 min in an occluded blood field). Patency of the treated vein segments was tested with completion venography at the end of the procedure (Figs 1 and 2). Residual stenosis found at either femoral or iliac vein segments was treated with balloon angioplasty followed by venous self-expanding stent application. At the end of lysis/aspiration process, the introducer sheath was removed followed by manual compression for at least 15–20 min for the access vein site. Success of the procedures was defined as restoration of antegrade flow in the treated vein segments with complete or partial (≥90%) removal of the occlusive thrombus and disappearance of any detected residual and/or underlying stenotic lesions. Low-molecular-weight heparins (LMWHs) like enoxaparin were administered following the procedure in full therapeutic doses for 10 days with dose adjustment made according to the individual body weight (1 IU/kg). Oral anticoagulation with vitamin K antagonists was done followed by the short course of LMWH therapy and continued for at least 6 months with necessary dose titration made to achieve international normalized ratio (INR) values of 2–3. All DVT patients with cancer received LMWH

Figure 1



A case of right iliac vein acute thrombosis before (right) & after (left) pharmacomechanical thrombolysis.

Figure 2



A case of right ilio-femoral vein acute thrombosis before (right) and after (left) pharmacomechanical thrombolysis.

therapy alone postoperatively. Patients in whom venous stents were used were additionally given clopidogrel (75 mg once daily) for 3 months after the intervention. All patients were discharged after the intervention when ensuring no local or systemic complication from thrombolytic drugs. The temporary vena cava filters were routinely removed within 30 days after the procedure from the contralateral common femoral vein approach with a special retrieval kits even with an INR level of 2–3 and only after ensuring that there were no further risks of PE.

Follow-up

Physical examination and venous duplex ultrasound were carried out on the next day after the procedure and then at 3 and 6 months postoperatively to check for patency of the treated venous segments and any lower limb manifestations. All patients were kept on oral anticoagulation with warfarin with necessary regular check of INR every 3 weeks at outpatient clinic department.

Results

A total of 25 patients presented with an acute unilateral lower limb ilio-femoral DVT were selected for PMT. The average age of patients was 45 years (range: 28–64 years). There were 13 (52%) females and 12 (48%) males. The extent of venous thrombosis was up to the common femoral vein in five (20%) extremities and up to the common iliac vein in 17 (68%) extremities with three (12%) extremities diagnosed with isolated iliac vein thrombosis. All patients had moderate to severe lower limb pitting edema, 23 (92%) patients had dull aching or heaviness leg pain, three (12%) patients had marked swelling with pallor (phlegmasia alba dolens), whereas one (4%) patient had significant swelling with cyanosis (phlegmasia cerulean dolens). A total of five (20%) patients had an active cancer disease in the form of breast cancer in three patients and colon cancer in two patients. The clinical characteristics of all patients are shown in Table 1. Additional adjunctive procedures, including balloon angioplasty of residual vein stenosis with venous stent placement, were required in three (12%) patients. Vascular stent placement was made in the common and/or external iliac veins for management of residual stenosis using the self-expanding stent (Wall stent; Boston Scientific Vascular). One patient with isolated common iliac vein thrombosis was suspected to have May–Thurner syndrome (MTS) as the reason for isolated left common iliac vein stenosis and underwent stent placement. The important details of the operative procedures and outcomes are shown in Table 2. We have used the AngioJet device for PMT and use rTPA (e.g. Alteplase: 1 mg/ml) as the thrombolytic agent used for thrombolysis, and the procedure was found to be angiographically successful in 21 (84%) patients

Table 1 Clinical characteristics of patients

Presentation	*n* (%)
Symptoms	
Swelling	25 (100)
Pain	23 (92)
Phlegmasia alba dolens	3 (12)
Phlegmasia cerulea dolens	1 (4)
Side involved	
Right	11 (44)
Left	14 (56)
Interval since symptom onset	
1–7 days after symptom onset	20 (80)
After the first week	1 (4)
14 days after symptom onset	4 (16)
Coexistent malignancies	
Colon cancer	2 (8)
Breast cancer	3 (12)
Extension of deep vein thrombosis	
Ilio-femoral DVT	17 (68)
Common femoral –femoral DVT	5 (20)
Isolated iliac vein thrombosis	3 (12)

DVT, deep vein thrombosis.

Table 2 Perioperative data of patients

Successful thrombus lysis (>90%)	21 (84)
Additional procedures	
Balloon angioplasty with stenting	3 (12)
Patency of treated veins	
At 1st month	21 (84)
At 6th month	19 (76)
Postoperative complications	
Minor bleeding	2 (8)
Major bleeding	1 (4)
Access site hematoma	4 (16)
Extravasation	1 (4)
Route of IVC filter insertion	
Contralateral femoral vein	25 (100)
Postprocedure secondary complications from DVT	
Residual limb edema (mild to moderate)	13 (52)
Severe (incapacitating) edema	0%
Secondary varicose veins	2 (8)
Leg skin pigmentation	2 (8)
Chronic limb pain	9 (36)
Venous ulceration	0
Chronic deep veins insufficiency	2 (8)

DVT, deep vein thrombosis; IVC, inferior vena cava.

(>90% of the thrombus was removed). In the remaining four cases, failure was either due to patient intolerance during the procedure, inability to cross the occluded segments by the guide wire, or difficulty in obtaining the popliteal vein access due to morbid obesity with severe limb edema, and they were all managed by standard anticoagulation therapy alone with local and systemic anti-edema measures. In all successfully done cases (84%), patients required no more than one catheter-laboratory session. The average duration of the whole intervention was 90 min (range: 45–240 min), and the site of venous access was the ipsilateral popliteal vein in all patients. Major bleeding events occurred in only one (4%) patient (cancer patient) and was managed by blood transfusion and colonoscopy. The overall in-hospital stay duration was at a median of 3 days (2–7 days). Follow-up after discharge was done at vascular outpatient clinic every month for a period of 6 months. Follow-up duplex ultrasound was done at the first and 6 month and revealed patency of the treated vein segments in 21/25 (84%) patients at first month and in 19/25 (76%) patients at 6 months. Thrombus recurrence was observed in two patient who were managed by anticoagulation therapy alone. The number of postthrombotic limb complications discovered during the follow-up period was moderate nondisabling chronic lower limb edema in 13 (52%) patients, leg skin pigmentation in two (8%) patients, chronic (mild to moderate) lower limb pain in nine (36%) patients, and secondary varicose veins in two (8%) patients both were with underlying incompetent deep veins. The total lower limb deep vein patency rate was 76% at the final follow-up visit.

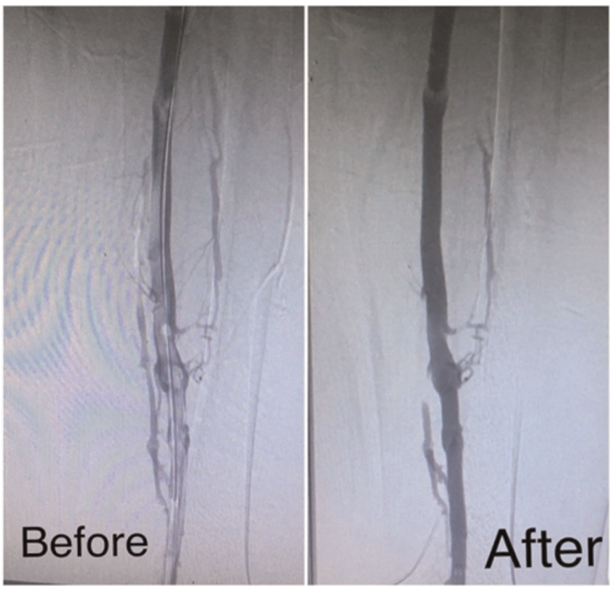
Discussion

The current standard of care for acute lower limb DVT despite being controversial, depends largely on short-term of parental anticoagulation with heparins during the acute phase followed by therapy with vitamin K antagonists for a variable duration depending on presentation and associated comorbidities [9,16]. Although being efficient in decreasing the risk of PE, this regimen of therapy with anticoagulation is still inadequate in preserving or restoring the function of venous valves which is the main reason for developing PTS, because anticoagulation drugs do not remove the occlusive thrombus but venous patency is restored later via intrinsic fibrinolytic mechanisms [3,4]. Early removal of the occlusive thrombus via thrombolysis or thrombus aspiration could be done via catheter-based techniques, which offers the value of preserving the structure of venous valves with resultant avoidance of possible PTS [9,10,17]. Various recent catheter-based techniques have been extensively studied in management of lower limb DVT, including mechanical thrombectomy and CDT followed by adjunctive procedures like balloon angioplasty with or without venous stenting. CDT proved effective in removing ilio-femoral DVT; however, it is not widely utilized because of the anticipated risks of hemorrhage and the lack of robust data from well-conducted prospective, randomized trials [11,12]. Ouriel *et al.* [18] in their study compared urokinase versus rTPA for CDT in 653 patients with acute lower limb DVT. Results demonstrated significant bleeding in 12.4 versus

22.2% of patients, respectively; and intracranial hemorrhage in 0.6 versus 2.8% of patients, respectively. During the course of our study, we have encountered no significant bleeding complications or intracranial hemorrhage and only one patient required blood transfusion for postprocedure bleeding per rectum that was soon controlled by colonoscopic procedure. Another two patients had minor bleeding that stopped spontaneously after short time of manual compression and four other patients developed small hematoma at the access site mostly from insufficient manual compression and resolved spontaneously. These hazards of CDT have stand against its universal use, but they may be ameliorated by the more recent technique of PMT that combines the use of CDT and mechanical thrombectomy with significant higher success rate exceeding that of mechanical thrombectomy alone (62.4 vs. 26%) [17]. These improvements in successful thrombus removal have led to general suggestion that CDT should be used together with mechanical thrombectomy provided no contraindications for thrombolysis [19,20]. However, still mechanical thrombolysis alone without CDT could be used whenever there is a contraindication of thrombolysis with good results achieved in many studies [21–23]. The AngioJet device that we used in this study uses combinations of mechanical dissolution and thrombolysis followed by aspiration of thrombolysis debris [24]. The advantages of combining the use of mechanical thrombectomy and thrombolytic therapy in thrombus removal include the rapid fragmentation of thrombi over a short time with use of small dose of thrombolytic drugs [14]. An overview of the pathogenesis of PTS will reveal that rapid and complete fragmentation of thrombus is the most important objective of PMT technique to avoid this incapacitating complication [25]. The AngioJet produces multiple jets of pulsatile saline flow in a retrograde direction to create a localized low-pressure zone for easy and rapid thrombus maceration and aspiration. Selection of patients to undergo PMT was based on the American College of Chest Physicians suggestions [16]. Overall, three patients with isolated common iliac vein thrombosis were selected for the procedure, and one of them was suspected of having MTS as the underlying cause of iliac vein lesion which is the most common cause of left common iliac vein compression in the literature. Despite the relatively high incidence of this syndrome, the clinical prevalence of MTS-related DVT is surprisingly low [26,27].

Like all other similar devices used in catheter-based thrombolysis, PE remains a possible hazardous risk during the thrombolysis procedure [28], and the recently published American College of Chest Physicians guidelines for catheter-based thrombolysis techniques have suggested the adjunctive use of a temporary IVC filters to ameliorate this risk [21]. We have used retrievable IVC filters inserted via contralateral transfemoral approaches. According to the manufacture's instruction of use, these filters can be retrieved from femoral vein approach after a certain period of time up to 60 days. We routinely removed the IVC filters during the first month after PMT even with an INR level of two to three provided that there were no clinical or laboratory evidence of pulmonary emboli or any attendant risk of further PE. In our study, we encountered no significant problems during IVC filters insertion or removal, and all filters were successfully removed from common femoral vein approach using special retrieval catheters provided by the manufacturer.Our technical success rate was high as compared with other similar studies despite our small sample size. In our present analysis, all successfully treated 21 patients had complete restoration of venous flow and complete or near complete thrombus removal, representing 84% technical success rate (21/25 patients). We could not successfully remove the thrombus in four (16%) patients because of old clot formation due to late intervention time from the onset of the symptoms. We realize that this success rate, however, appears to be lower than that recently reported by Köksoy *et al.* [29], which could be attributed to the small number of patients in our study owing to the high cost of the procedure together with the adjunctive interventions (Fig. 3).

Figure 3



A case of left femoral vein acute thrombosis before (right) and after (left) pharmacomechanical thrombolysis.

Regarding the optimal time for thrombus removal, according to the literature, the successful thrombus removal in patients with acute DVT is achieved in those with recent DVT symptoms lasting less than 10 days [16,17,21]. In our study, the most common selected time interval between onset of DVT symptoms and intervention is within the first 7 days. After 14 days or more from onset of DVT symptoms, the success of thrombus removal is reduced [29]. Comparative studies with larger patient series are still needed to further validate this observation; however, until results of such studies, we do not advocate trial of PMT in patients with acute limb DVT lasting beyond this time interval except on individual basis.

New Oral AntiCoagulants (NOACs) were not used in those patients because a lot of patients enrolled in the study were having no covering medical insurance that makes long-term postoperative NOACs incur some financial burden, to standardize the management to all patients to avoid statistical bias in results, we choose to give the commonly available oral anticoagulants available for all patients (vitamin k antagonists).

We know that PTS manifestations often take longer time to arise, although this is strongly variable with no definite time frame known in most of published studies that we revise. But we choose to follow-up our cohort of patients over this short period because we are examining the short-term results of the procedure. Longer follow-up will probably need larger sample size, and we considered this point one of the limitations of our study and we referred to it in the section of our study limitations in the thesis discussion.

The technical success rates of PMT are further enhanced by the additional adjunctive endovascular procedures. In our series, interventions such as angioplasty and stenting have been performed in 3/21 (12%) patients owing to residual stenosis. As regarding procedural complications, in our study, no major perforation or retroperitoneal hemorrhage was seen. In one case, a small transmural perforation was detected and stopped spontaneously. Our follow-up analysis of postprocedural limb manifestations has shown success of PMT to prevent the severe clinical forms of PTS in a short-term, despite the incidence of 52% mild-to-moderate limb edema that has been controlled by compression elastic stockings. Improved patency of the ilio-femoral venous system at 1 and 6 months (84 and 76%, respectively) was evident on venous duplex scanning of the target limbs. With the ever-increasing improvements in interventional techniques that usually comes with the increasing use of such endovascular technology of PMT followed by anticoagulation, these outcomes could substantially improve in terms of improved venous patency, preserved valves functions and lowering the incidence of PTS with overall increase in quality of live parameters, especially if large patient samples will be enrolled after wide availability and wider adaption of the technique in the near future. Our study has focused primarily on the feasibility and safety of this techniques to set up the stage for bigger future studies.

Conclusion

Early thrombus removal with PMT is considered a safe and effective treatment tool for selected cases of acute lower limb ilio-femoral DVT. However, further randomized controlled trials on larger patient's population are required before advocating the wide adoption of this new technique for management of acute lower limb DVT.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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