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Pharmacomechanical catheter-directed thrombolysis for acute iliofemoral deep vein thrombosis: our case series

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Abstract. – OBJECTIVE: This is a retrospective study on Pharmacomechanical Catheter-Directed Thrombolysis (PCDT) in the treatment of acute iliofemoral Deep Vein Thrombosis (DVT).

PATIENTS AND METHODS: From March 2013 to November 2016, 22 patients (26 limbs), median age 46.7 years with acute (<21 days) extensive iliofemoral DVT underwent Percutaneous Mechanical Thrombectomy (PMT) with Aspirex (Straub Medical, Wangs, Switzerland), followed by Catheter-Directed Thrombolysis (CDT). Subsequent endovascular stenting was performed for underlying obstruction. The follow-ups were conducted up to 1 year, in two Centers by experienced operators. Post-Thrombotic Syndrome (PTS) was evaluated by assessing the Villalta Scale (VS) and measuring orthostatic venous pressure.

RESULTS: Post-operative iliofemoral vein patency was restored in almost all cases (95.5%). Standard urokinase dose was 80.000 IU per hour; mean infusion time was 32.5 hours. Stenting was performed in 15 cases (68%). Median follow-up was 19.9 months (6-48 months); 21/22 patients completed the 12 months follow-up. At 30 days follow-up symptoms disappeared in 21/22 cases (95.5%), with one case (4.5%) of DVT recurrence. At 1-year follow-up there were 3 cases (14.2%) of mild PTS; 18 patients (85.8%) were free from PTS. At 1-year follow-up venous pressure measurement showed normal values in 11 cases (52.4%), mild hypertension in 7 patients (33.3%), moderate hypertension (80-100 mmHg) in 2 cases (9.5%) and severe hypertension (110 mmHg) in one case (4.8%). Neither major nor minor complications were observed.

CONCLUSIONS: PMT with Aspirex combined with CDT with urokinase seems to be a safe and effective treatment for acute iliofemoral DVT and it shows promising results in reducing the risk of PTS. Thus, we suggest a controlled trial with this treatment strategy.

Key Words
Deep venous thrombosis, Pharmacomechanical Catheter-Directed Thrombolysis, Post-thrombotic syndrome, Aspirex, Venous stenting.

Introduction

Over the last few decades new treatment strategies have been developed for the treatment of chronic venous disease[1] and acute iliofemoral Deep Vein Thrombosis (DVT)[2]. Reported annual incidence for DVT varies from 45 to 117 per 100.000 person-years[3] with a risk of developing Pulmonary Embolism (PE) ranging from 20% to 50%[4]. The current recommended treatment of acute DVT is anticoagulation for a period ranging from 3 to 6 months[5] with the purpose of preventing thrombus extension or embolization. Despite prompt anticoagulant therapy the risk of developing Post-Thrombotic Syndrome (PTS) ranges from 20% to 50% within 2 years of symptomatic DVT[3,4]. PTS is a long-term complication of DVT with a huge impact on quality of life and health care costs[6]. It is characterized by feelings of heaviness, cramps, chronic pain, swelling of the affected limb and, in 5-10% of cases, venous ulcers. In the case of common femoral or iliac vein thrombosis, venous claudication, pain and ulcers are significantly more severe[7] and frequent[8-11]. Thus, the attempts for early thrombus removal in acute iliofemoral DVTs have been solicited to preserve valvular function and avoid post-thrombotic morbidities. The benefits of early thrombus removal in terms of a reduced incidence of PTS have been demonstrated since the introduction of surgical thrombectomy[12]. Catheter-Directed

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Thrombolysis (CDT) showed good results in terms of clot reduction and patency rates but increasing major bleeding risk[13]. Recently, data coming from the CaVenT study showed better outcomes in terms of patency of ileo-femoral DVT, comparing CDT to standard treatment[14]. Furthermore, the 5 years follow-up showed a significant (28%) reduction in the risk of developing PTS[15]. Pharmacomechanical Catheter-Directed Thrombolysis (PCDT) represents a further step in the treatment of DVT. In this procedure, the reduction in thrombus burden is achieved by Percutaneous Mechanical Thrombectomy (PMT) combined with CDT. Among the advantages of PCDT over CDT alone are the enhancing effects on thrombolysis, with a significant reduction in lytic doses, shorter procedure times associated with a reduction in radiation doses and fewer bleeding complications[16]. Various thrombolytic agents and devices have been used to treat proximal DVT, but the effect of different treatment strategies is inconclusive[17]. In our retrospective study we describe the safety and efficacy of PMT using the Aspirex device plus a standard dose of urokinase for a short time in the treatment of acute iliofemoral DVT, assessing its effect on the development of PTS and venous hypertension, to examine the feasibility of a controlled randomized trial.

Patients and Methods

Patients

We retrospectively analyzed the data of 23 patients (13 women, 10 men; age: 31-87 years; mean: 46.7 years) with acute iliofemoral DVT, who were treated in "S. Giovanni-Addolorata", Hospital, Rome, Italy, and submitted to follow-up in two different Centers by expert physicians from March 2013 to November 2016.

Inclusion criteria were as follows:
- DVT-symptom onset not prior to 21 days;
- absence of contraindications to thrombolysis;
- good functional status or life expectancy of more than 6 months.

The exclusion criteria were:
- contraindications for anticoagulant therapy or thrombolytic drugs;
- recent major surgery or cerebrovascular accidents;
- anticipated long-term bed rest.

DVT affected one side (left 15, right 3) in 18 patients; 4 cases show bilateral involvement. DVT extended to the inferior vena cava (IVC) at the time of diagnosis in 6 patients. PE was detected in 7 cases, two of which were massive. DVT-symptoms were swelling (22 patients) and pain (19 patients) of the affected leg. Predisposing factors for DVT were previously diagnosed malignancy (8 patients), thrombophilia (3 patients), May-Thurner syndrome (3 patients), estroprogestinic therapy (3 patients), recent surgery of the great saphenous vein (2 patients), recent appendicitis (1 patient). In two patients we did not observe risk factors or a predisposing cause for DVT.

The diagnosis of DVT was made using Color-Doppler Ultrasound (CDUS) followed by Computed Tomography scan (CT scan), to assess the proximal extension of thrombus and potential presence of PE. Anticoagulation was initiated upon referral and consisted of systemic heparinization in all cases. Informed consent was obtained from all patients.

Procedure

A 25 cm long 11 Fr introducer was placed in the femoral vein of the affected limb, after ultrasound-guided puncture of the vessel. Confirmation of DVT-diagnosis was obtained via venography. An initial intravenous bolus of urokinase (200.000 IU) was administered to all patients. A 0.035" stiff guidewire (Terumo Europe NV, Leuven, Belgium) was advanced through the thrombosed vessel up to the patent IVC. A 4 Fr diagnostic Vertebral catheter (Cordis Corporation, Miami Lakes, FL, USA) was passed over the wire and a phlebography of the IVC was performed. The 0.035" stiff guide wire was then exchanged for the 0.025" Aspirex dedicated guide wire and the 10 Fr thrombectomy catheter was put into place. After connecting the system to the motor drive the device was gently pushed into the thrombus and a thrombectomy was performed. According to the manufacturer's instructions for use, the Aspirex device was slowly advanced and retracted within the thrombosed vessel. Briefly, the mechanism of action of the Aspirex consists of a wall-contact thrombus aspiration via the slit placed in the distal tip of the catheter, the fragmentation of the clot through a rotating stainless steel spiral in the catheter lumen and, finally, the transportation and discharging of the macerated thrombus out of the patient's body into a plastic see-through bag, which allows the operator to continuously assess the blood-volume extracted from the patient. The femoral introducer must be irrigated by a continuous infusion of saline solution to prevent clots from obstructing the lumen device.

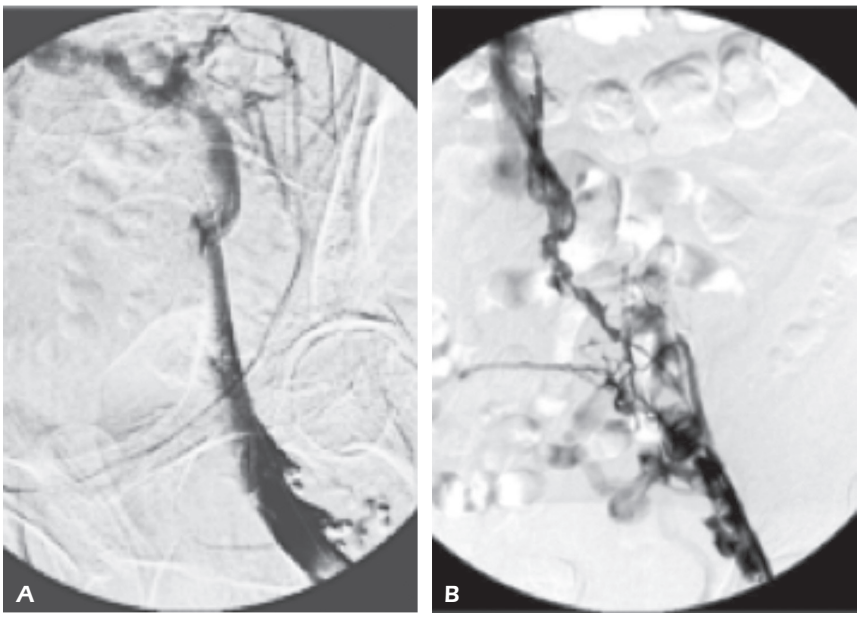

Figure 1. A-B, Venography shows occlusion of iliofemoral vein with collateral route toward the inferior vena cava.

Percutaneous thrombectomy was repeated several times, until the venogram showed partial recanalization of the vessels. At this point a multi side hole infusion catheter (McNamara 5 Fr, ev3, Maastricht, The Netherlands) was advanced into the vein and left in place. Overnight thrombolysis was administered through the catheter at a dosage of 80.000 IU per hour. The fibrinogen level was checked every 6 hours after urokinase infusion to maintain it above 100 mg/dL. After a mean interval of 12 to 24 hours the patient has referred to the Angio suite again and a venography check was performed. If a significant residual amount of thrombus was detected, the CDT was delayed and the patient was checked again in the Angio suite the following day (Figures 1-2). Angioplasty and venous stent placement were performed to complete the treatment if stenosis more than 50% was present (Figures 3-4).

When PE was present, a temporary vena cava filter (Denali, Bard Peripheral Vascular, Tempe, AZ, USA) was placed via the right internal jug-

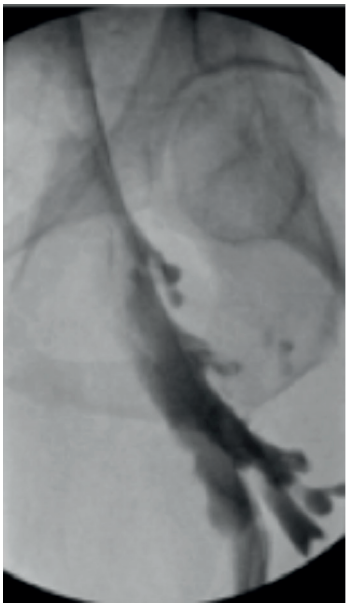

Figure 2. Introduction of Aspirex after puncture of femoral vein.

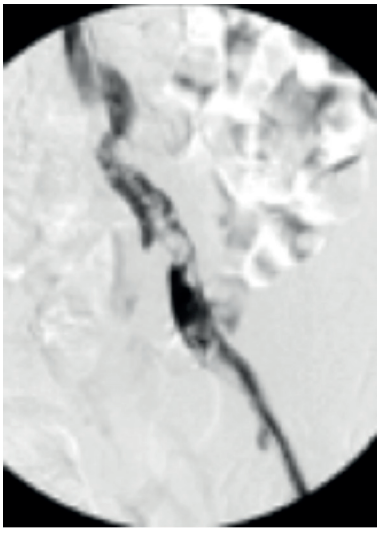

Figure 3. Venograms after PMT how residual thrombosis of common iliac vein and external iliac vein.

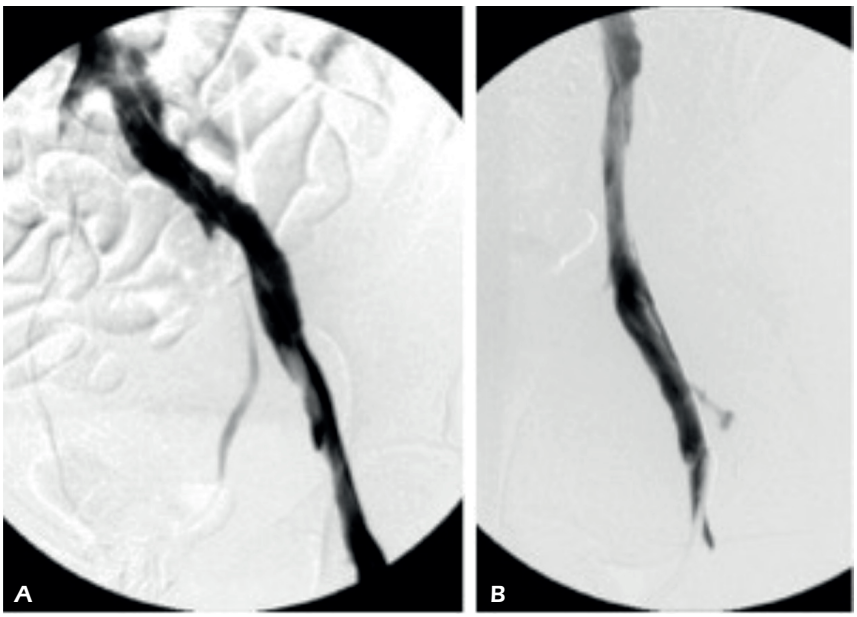

Figure 4. A-B, Venography after angioplasty and stenting shows patency of external iliac vein and common iliac vein.

ular vein, in order to prevent detached clots from reaching the pulmonary arteries and possibly worsening the hemodynamic conditions during the procedure. In the 4 patients with bilateral iliofemoral DVT, the treatment was first performed on the more severely affected limb and then, after the flow was restored on one side, the other limb was approached. This strategy allowed us to maximize the effect of thrombolysis, administering full doses of urokinase on each side.

Medical Therapy

After the procedure, according to guidelines, oral anticoagulation therapy was initiated for a minimum of a three-month period. At the end of anticoagulant treatment patients, undergoing iliac-femoral stenting, began life-long daily low-dose (100 mg) of aspirin. Furthermore, all patients wore elastic compression stockings, providing from 30 to 40 mmHg of pressure, for at least 6 months.

Follow-Up

Follow-up was performed in two different Centers with the same standardized guidelines by CDUS and clinical evaluation at 1 and 12 months from treatment and then on a yearly basis. PTS was clinically evaluated at the 12-month follow-up, using the Villalta Scale and, in the same session, orthostatic venous pressure was measured with a non-invasive technique. Final venous pressure values were determined by taking the median results of three measurements.

Villalta Scale

The Villalta Scale is a clinical scoring system which allows PTS to be both diagnosed and graded in severity. Symptoms (leg heaviness, pain, cramps, itching, paresthesia) and clinical signs (redness, hyperpigmentation, skin induration, pretibial edema, venous ectasia and pain during calf compression) are evaluated and points are given for each of these 11 items. According to severity, the score may range from 0 (absence of the specific sign/symptom) to 3 (severe). A total score of 5 to 9 denotes mild disease, 10-14 moderate, and >15 severe. The presence of an ulcer marks PTS as severe. Given its extensive use in clinical studies and since it has been shown to have a correlation with patient-perceived life quality[18,19], the Villalta Scale is considered a reliable and valid tool for assessing treatment effectiveness[20].

Non-Invasive Venous Pressures Measurement

The pathophysiology of PTS is basically based on venous hypertension, which follows either venous valvular incompetence or persistent obstruction due to failed recanalization of the deep thrombosed vein[21,22]. Valvular incompetence is a common consequence of acute DVT, as a result of direct damage to venous valves which occur in the thrombosed vessel or even in uninvolved distal veins, due to the hypertensive status and dilation of those vessels.

Using Bartolo's technique[23], venous pressure is measured by inflating a pneumatic cuff around the

ankle of the patient, holding a sphygmomanometer over the posterior tibial vein (PTV), while a CW Doppler probe at 8 MHz is placed underneath it. Final venous pressure values were determined by taking the median results of three measurements. In normal subjects, orthostatic venous pressure measurement values at the PTV are slightly lower than 60 mmHg; pressure values from 60 to 80 mmHg define a condition of mild venous hypertension, 80 to 100 mmHg moderate and >100 mmHg severe. In patients suffering from PTS, both superficial and deep venous pressure exceeds 100 mmHg and, in the presence of ulcerations, calf pressures can be found up to 120 mmHg[23].

Complications

The definition of complications was consistent with the standardized terminology and with the classification criteria suggested by the Society of Interventional Radiology (SIR)[24]. Major complications were defined as events that, if left untreated, could be life-threatening, result in a prolonged hospital stay or lead to permanent adverse sequelae, such as symptomatic pulmonary thromboembolism, intracranial hemorrhage or gastrointestinal ulcer bleeding. Minor complications were defined as those with no significant clinical sequelae and requiring no or minor therapy, such as local puncture site bleeding.

Results

Patients' demographics and clinical outcomes are reported in Table I and Table II. Briefly, whole patients except one (95.5%) showed patency at 12 months follow-up. Seven patients died of cancer, 6 patients in the period between the first and the second year following treatment and 1 patient 27 months after the treatment, respectively. Mean follow-up was 19.9 months (from 6 to 48 months). Post-procedural patency and were achieved in all patients (100%). Moreover, symptoms improved in the days following PMT and at discharge all patients were paucisymptomatic or asymptomatic. In 15 patients (68%), venography after PMT showed residual stenoses which were treated by angioplasty and stenting (Zilver Vena, Cook Medical Inc., Bloomington, IN, USA). The stenoses involved both the common and the external iliac veins in 6 patients, in the remaining patients the stenoses involved the common iliac vein in 5 cases, the external iliac vein in 2 cases and the common femoral vein in the last 3 cases,

Table I. Patient demographics.

Variable	No.	Percentage Value
Sex (M/F)	10/12	
Age (y)		
Mean, (Range)	46.7 (31-87)	
Symptoms		
Leg swelling	22	100%
Pain	19	86%
Side		
Left limb only	15	68.2%
Right limb only	3	13.6%
Bilateral	4	18%
Involved vessels		
Common femoral vein	19	86.4%
External iliac vein	18	81.8%
Common iliac vein	14	63.6%
Inferior vena cava	6	27%
Predisposing factors		
Cancer	8	36.4%
Thrombophilia	3	13.6%
Estroprogestinc therapy	3	13.6%
Recent saphenectomy	2	9.1%
May-Thurner syndrome	3	13.6%
Appendicitis	1	4.5%
Unknown	2	9.1%
Pulmonary embolism	7	31.8%
Ivc filter	7	
Removed after PMT	6	
Urokinase infusion time (hours)		
Mean	32.5	
Urokinase dose (million IU)		
Mean	2.6	
Follow-up duration (months)		
Mean, (Range)	19.9 (6-48)	

respectively. The implanted stent size varied between 12 mm for the common femoral vein and 16 mm for the common iliac vein. In all cases stent placement was followed by angioplasty in order to properly dilate the stent and avoid acute rethrombosis. In 3 cases the venography revealed segmental stenosis of the left proximal common iliac vein, which was attributed to May-Thurner syndrome, in the absence of other recognizable causal factors. All three patients were treated by stenting and angioplasty.

At the one-month follow-up clinical examination showed DVT-related symptoms disappearance in 21/22 patients (95.5%): one patient (4.5%) experienced a recurrent DVT of the common iliac vein with pain and swelling of the affected limb. He refused to repeat PMT and was treated with medical therapy alone. At the 12 months follow-up, twenty-one patients (95.5%) showed pa-

Table II. Clinical outcomes at 1-year follow-up.

Variable	No.	Percentage Value
Patency (pts)	21/22	95.5%
Villalta Score		
Mean, (Range)	3.1 (0-8)	
Post-thrombotic Syndrome (Villalta score)		
Absence (0-4)	18/21	85.8%
Mild (5-9)	3/21	14.2%
Moderate (10-14), Severe (>15)	0	
Venous pressure (mmHg)		
Mean, (range)	68.5 (60-110)	
Normal (<60 mmHg)	11	52.4%
Mild hypertension (60-80 mmHg)	7	33.3%
Moderate hypertension (80-90 mm Hg)	2	9.5%
Severe hypertension (>90 mmHg)	1	4.8%
Stenting (limbs)	15	
Common + external iliac vein	6	
Common iliac vein	5	
External iliac vein	2	
Common femoral vein	2	

tency of the treated vessels as detected by CDUS. Villalta scores were between 6 and 8 in 3 out of 21 patients (14.2%), showing a mild PTS condition, while in 18 out of 21 patients (85.8%) values were <4, showing no post-thrombotic disease at all. Among the 3 patients suffering from mild PTS, one experienced recurrence of DVT and two showed patency of the treated vessels during follow-up. Non-invasive venous pressure measurements showed normal values (<60 mmHg) in 11 cases (52.4%), a mild venous hypertension (70 mmHg) in 7 cases (33.3%), moderate hypertension (80 to 90 mmHg) in 2 cases (9.5%) and finally, in one patient (4.8%) who experienced rethrombosis, measurements showed a venous pressure of 110 mmHg, which indicates severe venous hypertension. We did not observe major nor minor complications in our study.

Discussion

Nowadays preventing the extension of acute iliofemoral thrombus, avoiding pulmonary embolism and post-thrombotic syndrome, still remains the main goal in patient's treatment. The strongest predictive factors in developing PTS are the persistence of residual symptoms in the affected limb at 1 month after DVT, in relation to partial recanalization of the thrombosed segment and primary involvement of the iliofemoral tract. Twenty-four percent of all lower limb DVTs involve the iliofemoral segment[4]. In these cases, the obstruction of the iliac axis and common femoral vein causes a severe outflow blockage by hampering the activation of major collateral route of the lower limb, represented by the deep femoral vein[25,26]. Currently, anticoagulants are the mainstay of treatment for DVT[5]. However, the evidence demonstrates that patients with iliofemoral DVT treated with only medical therapy suffer from severe post-thrombotic morbidity[9], with symptoms such as venous claudication or ulcers[8,11]. Data supporting the "open-vein hypothesis" have been available for over two decades, showing improved rates of patency and a reduction in swelling, venous hypertension and risk of PTS, compared to anticoagulation alone[27]. CDT has been proved to provide initial clinical success in 80% of cases, with iliofemoral patency rates at 1 year ranging from 40% to 78%, depending on the studies evaluated[13,28]. Nonetheless, this technique is burdened by high hemorrhagic risk, with major bleeding occurrence in those studies varying from 5% to 11%[29,30]. PCDT adds mechanical clot reduction to the pharmacological effect of thrombolytic agents. It results in the use of smaller doses of urokinase, with a reduced hemorrhagic risk, compared to CDT alone[31]. The positive findings of the 5-years CaVenT (Catheter-Directed Venous Thrombolysis) trial follow-up[14,15] are not confirmed by a recent large trial on the pharmacomecanical treatment of the acute iliofemoral vein thrombosis (ATTRACT trial)[17].

Differences between the two trials include the larger size of the former (209 *vs.* 692 patients), its geographic and demographic scopes (4 Norwegian centers *vs.* 56 U.S. centers), and the longer rt-PA infusions used in the CaVenT trial *vs.* the greater use of mechanical therapies in the ATTRACT trial. On the contrary, smaller but well-selected studies based on the combination of PMT and CDT confirm our findings, with good short and intermediate-term clinical outcomes and without relevant side effects[32]. Moreover, a recent sub-analysis of the ATTRACT trial on 391 patients with isolated iliofemoral DVT showed positive findings. In this trial, PCDT significantly reduced early leg symptoms and, over 24 months, reduced PTS severity scores, reduced the proportion of patients who developed moderate or severe PTS, and resulted in greater improvement

in venous disease-specific Quality of Life (QoL)[33]. Our work showed some original characteristics. In our experience, the median dose of urokinase administered was 2.6 million IU, much lower than the mean reported dose (7.8 million) administered in reported CDT studies, as was mean infusion time (32.5 hours), shorter than those described (53.4 hours)[13]. Therefore, we did not report any complication. At the 1-month follow-up, 95.5% of the patients were asymptomatic: this data aligns with the results described by other PMT experience[34-38]. Patency rates during follow-up in our study were 95.5%: we observed a recurrence of thrombosis in 1 patient (4.6%). According to previously published papers[39-41], recurrent DVT after PMT may occur in up to 13% of patients. Patency after stenting was 93.3%, a result that was similar to those published before[42,43]. Since Villalta Scale is partly based on subjective data, such as symptoms perceived from the patients, we decided to include venous pressure measurement at the 12-month follow-up to have an adjunctive instrumental parameter to evaluate PTS. Thus, the presence and severity of PTS were evaluated in a complementary way[20,23]. At the 12-month follow-up we observed 3 cases of mild PTS (14.2%): two patients had, respectively, Villalta scores of 6 and 7 with patency of the treated vessels at CDUS examination. In these two patients, non-invasive venous pressure measurement showed moderate hypertension (respectively, 80 and 90 mmHg). The patient who experienced re-thrombosis at 1 month, who was subsequently treated with anticoagulation alone, showed a partial recanalization at 12-month CDUS, a Villalta score of 8 and venous pressure at the ankle of 110 mmHg. Thus, PTS rates among our patients are similar to those observed in other studies[16,44,45], varying from 5.6% to 18%. Finally, even though our work presents limitations, including the small size and retrospective design approach, we obtain strict adherence of the studied sample to follow-up controls performed by the same operators every time. Moreover, our study included patients all treated in a single expertized center with the same therapeutic strategy approach. A further step of our work is to complete the collection of the data of the 5 years follow-up.

Conclusions

We found that percutaneous pharmaco-mechanical thrombolysis appears a safe and effective technique for the treatment of acute iliofemoral deep venous thrombosis and it showed promising results in reducing the risk of developing the post-thrombotic syndrome. The key points of our findings, in comparison with other recent data, are the strict selection of patients confined to those with only acute iliofemoral thrombosis, the use of the Aspirex device combined with a standard low dose of urokinase for a short time and the absence of complications. Thus, long-term prospective controlled trials enrolling a larger sample of patients and longer follow-up, currently not present in literature, seem worthwhile.

Ethics Approval Statement

For this type of study the Ethical approval is not required.

Conflict of Interests

The authors declare no conflict of interest.

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