Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis, a Prospective Randomized Controlled Trial

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ABSTRACT

Objectives: *To compare catheter directed thrombolysis plus standard anticoagulation with anticoagulation alone in patients who have acute iliofemoral vein thrombosis.* ***Patients and Methods:*** *Fifty patients with acute iliofemoral DVT were randomized in a 1:1 ratio to either CDT followed by anticoagulation (CDT group) or to anticoagulation alone (control group). Duplex ultrasound was used to assess patency and reflux of treated venous segment as well as to diagnose recurrence. Villalta score was used to assess the development of PTS.* ***Results:*** *After a mean follow-up duration of 10.78 months, data were available for 45 patients (22 patients had CDT plus anticoagulation, and 23 had anticoagulation alone). Four bleeding episodes were reported in relation to the 22 CDT procedures (18.18%) compared to two (8.7%) in the control group (P=0.09). Patients in the CDT group, when compared to the control group had significantly higher iliac vein patency rate (86.36% vs. 56.52%, P=0.027), and significantly less venous reflux (54.55% vs. 86.96%, P=0.016). The risk for the development of PTS was reduced by 20.36% (31.82% vs. 52.17%, P=0.016). In the CDT group, two patient (9.09%) suffered recurrent DVT, compared to a single patient (4.35%) in the control group (P=0.608).* ***Conclusion:*** *In acute Iliofemoral DVT, the addition of CDT to standard anticoagulation compared to anticoagulation alone is safe and tolerated by most of the patients. It resulted in better venous patency and competence. Yet, it did not appear to have an additional protection against re-thrombosis.*

Key Words: *Thrombolysis, Iliofemoral, Thrombosis*

INTRODUCTION

Following lower extremity DVT, as many as 20% to 80% of patients may have some degree of post-thrombotic long-term manifestations, such as pain, edema, heaviness, or hyperpigmentation. Severe post-thrombotic syndrome (PTS) occurs in 7% to 23% and ulceration occurs in 4% to 6% of patients [1]. It is believed that PTS results from ambulatory venous hypertension, which occurs with persistent venous obstruction and/or venous insufficiency after inflammatory destruction of valves in response to acute DVT[2]. Among several strategies for early thrombus removal, operative venous thrombectomy is not adopted by many vascular surgeons, except for patients who are not otherwise candidates for CDT or in medical communities where catheter-based techniques are not available [2],[3]. Systemic thrombolysis has the limitations of being associated with higher risks of bleeding complications, and high risk of failure in patients with extensive occlusive venous thrombosis. Catheter-directed thrombolysis (CDT) has emerged as an alternative endovenous treatment for DVT, and catheter-based techniques are now the preferred method of managing patients with extensive venous thrombosis if thrombus removal is desired. [2], [4].

There is no head-to-head studies comparing standard anticoagulation alone to additional CDT, except the CaVenT trial, which is a multicenter, randomized, controlled trial evaluating the long-term outcome of additional catheter-directed thrombolysis compared with standard treatment alone in patients with a proximal femoral or iliac vein thrombosis [5-7].

This study was conducted to determine whether the addition of CDT to standard anticoagulation, as compared to anticoagulation alone, would improve patency of the treated venous segments, reduce the incidence of recurrent venous thromboembolism (VTE) and development of PTS.

PATIENTS AND METHODS

This is a prospective, randomized, parallel two-arm, controlled clinical trial, comparing treatment of acute iliofemoral DVT with CDT plus standard anticoagulation versus standard anticoagulation alone.

We enrolled 50 consecutive patients who were admitted to Kasr Al Ainy medical school between November 2014, and January 2016, with duplex-verified first episode iliofemoral DVT. Patients eligible for inclusion were aged below 70 years, and had symptom onset within the previous 14 days. Patients were excluded if they met one or more of the exclusion criteria listed in **(Table 1)**. Patients were randomized in a 1:1 ratio using a50 numbers random number table generated by Stat Trek's Random Number Generator.

Table 1: Exclusion criteria

Bleeding diathesis	***Severe anaemia (haemoglobin<8 g/dL)***
Thrombocytopenia (platelets <80 000/mm^3)	Renal impairment (estimated creatinine clearance <30 mL/min)
Acute DVT during pregnancy or within 7 days postpartum	Within 14 days following major surgery or trauma
History of subarachnoid or intracerebral bleeding	Concomitant disease with life expectancy less than 24 months
Drug abuse or mental disease that could interfere with treatment and follow-up	Current malignant disease

Patients were prescribed anticoagulant therapy in accordance to local routines based on international guidelines using the low molecular weight heparin (LMWH) enoxaparin (Clexane®; Sanofi, France) in a dose of 1 mg/kg/12 hours, for at least five days. Oral warfarin (Marevan; GlaxoSmithKline, UK) was started the day of randomization for patients in the control group, and on the 2nd day post-procedure for patients in the intervention group, at a daily dose of 5 mg. The dose was modified according to the patient's international normalized ratio (INR) with a target INR of 2.0 to 3.0. LMWH was stopped when the patient's INR is 2.0 or above for at least 24 hours. Warfarin was continued for at least 3 months.Patients were prescribed sized to-fit, knee-high, 30 to 40mm Hg, graduated elastic compression stockings at hospital discharge for the intervention group, and at the 10th day follow-up visit for the control group.

Catheter directed thrombolysis:

CTD patients were scheduled for the nearest endovascular list.

In the prone position, and under local anesthesia, an 18 gauge- 9 cm needle was used to puncture the popliteal vein under ultrasound guidance. Popliteal vein access was established by advancing a 6-french sheath. A venography was then performed to determine the topography of the thrombus. A 0.035 inch 260 cm standard j-tip Terumo guidewire (Terumo Inc., Japan) was used to cross the thrombus to a healthy part of the IVC. When difficulty was encountered during crossing of the lesion, a stiff Terumo, 0.035" 260 cm wire was used. After adequate flushing with heparinized saline, a 4 or 5 French 90 cm length Fountain infusion system with Squirt (Merit Medical Systems, Inc. USA), with an infusion segment length of 50 cm, was advanced over the guidewire. We had used alteplase (Actilyse®; Boehringer-Ingelheim, Ingelheim am Rhein, Germany) as the thrombolytic agent in our series. Forceful injection of an initial dose of the thrombolytic agent (10 ml) was then performed. The patient was transferred to intermediate care unit where one ml of the thrombolytic agent was injected every hour by the squirt pump. Heparinized saline was infused in the sheath at a rate of 300 units per hour using a syringe pump throughout the treatment period. In the cath-lab, a venogram was then performed after 40 hours to determine the need for either continuation of thrombolytic therapy, repositioning of the catheter, or the need for venoplasty, and/or venous stents. Thrombolysis grade was calculated to define the effectiveness of thrombolysis in each patient of the CTD group. Where it represented the percentage reduction in the thrombus score after thrombolytic therapy was complete and can be deduced from the following equation;

$$Thrombolysis\ grade = (total\ thrombus\ score\ before\ CTD - total\ thrombus\ score\ after\ CDT) \div total\ thrombus\ score\ before\ CTD \times 100$$

Whereas, grade I thrombolysis (ineffective lysis) = ≤ 50%, grade II thrombolysis (partial lysis) = 50%-89% and grade III thrombolysis (complete lysis) = ≥ 90% were considered. Total thrombus score was obtained at the two intervention occasions, first prior to administration of the thrombolytic agent and second, after thrombolytic therapy was complete. For each vein segment; that is, IVC, the common iliac vein, the external iliac vein, the common femoral vein, the proximal and distal femoral veins, and the popliteal vein; the contrast enhanced image was optically examined and given a score from 0 to 2, where 0 = open vein, 1 = partially occluded vein, and 2 = completely occluded vein. At the end of the procedure, infusion catheter and sheath were removed and puncture site closure was established by manual compression for 20 min followed by compressive crepe bandage for further two hours, while the patient is immobilized. Patients were discharged home whenever there was no hematoma at the vein puncture site nor any suspicion of concealed hemorrhage and after initiation of warfarin therapy.

Follow-up:

Bleeding complications (procedure-related/ anticoagulation related) were recorded. Any bleeding that led to drop of more than 2 gm/dl of hemoglobin and/or necessitated blood transfusion was considered a major bleeding. Conversely, any bleeding that did not meet the abovementioned criteria was considered minor bleeding. Patients in both study groups were followed up at 10 days, 30 days and monthly thereafter for 6 months following the procedure. The patient was evaluated for the signs and symptoms of DVT and/or PE and PTS. We used both the Villalta score and the venous clinical severity score (VCSS) to assess for development of PTS. The patients were fully educated on the signs and symptoms of VTE and PTS. They were instructed to contact the study center immediately whenever any of these conditions occurred.

All patients were subjected to a venous duplex examination of the treated venous segments at 1 &6 months post-procedure and an any time a suspicion of PTS and DVT was raised. Recurrent DVT was considered to have occurred when a previously compressible vein segment turned to be non-compressible or a previously abnormal venous segment had a more than 5 mm increase in the diameter of the thrombus during full compression of the vein. Post-thrombotic iliofemoral wall thickening, residual thrombi, venous sclerosis and venous reflux were reported. Venous reflux was evaluated with the patient in the standing position, and was defined as reversal of the velocity curve lasting more than 0.5 second after distal compression. PE was suspected when there was one or more of the following: dyspnea, chest pain, cough, fever, hemoptysis or syncope. The diagnosis was confirmed by CT pulmonary angiography.

Data analysis:

Data were coded and entered using the statistical package SPSS version 23. Data was summarized using mean and standard deviation or median and interquartile range for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired t test in normally distributed quantitative variables while non-parametrical Mann-Whitney test was used for non-normally distributed quantitative variables [8]. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5 [9]. Correlations between quantitative variables were done using Spearman correlation coefficient[10]. Linear regression was done to detect VCSS using the Villalta score. Absolute risk reduction with its 95% confidence interval was calculated. P-values less than 0.05 were considered as statistically significant**.**

RESULTS

Demographic and clinical characteristics were similar between the patients in the two groups **(table 2)**. In the CDT group, complete lysis (grade III) was achieved in 15 patients (68.18%), and 50%–90% lysis (grade II lysis) in 6 patients (27.27%). Grade I lysis (ineffective lysis) occurred in a single patient (4.55%).Among patients who had complete lysis (15 patients), culprit stenotic lesions in the proximal common iliac vein were encountered in 14patients. All of these lesions were located on the left side. Balloon angioplasty was performed in the 14 patients. Stenting of the lesion was performed in

11 patients with self-expanding Wallstents® (Wallstent Endoprothesis; Boston Scientific, USA) **(figure 1)**. All the eleven stents were 14 mm diameter and their length varied from 70 mm (in 2 patients) to 90 mm (in the remaining 9 patients).

Table (2): Demographic and clinical characteristics among both the CDT and the control groups

	Catheter-directed thrombolysis group (n=22) N(%)	***Standard treatment only group (n=23) N(%)***	***P value***
Mean Age (years)±SD	40.25±11.42	42.5±12.03	0.548
Gender:			
▪ Men	5(22.73%)	6(26.09%)	0.793
▪ Women	17(77.27%)	17(73.91%)	
Duration of symptoms (days)	5.77±3.16	4.65±3.27	0.450
Left-sided deep vein thrombosis	18(81.82%)	17(73.91%)	0.722
Site:			
▪ Isolated pelvic deep vein thrombosis	2(9.09%)	0	0.457
▪ Iliofemoral deep vein thrombosis	5(22.73%)	7(30.43%)	
▪ Iliofemoropopliteal deep vein thrombosis	15(68.18%)	16(69.57%)	
Risk factor profile:			
▪ No risk factor for venous thrombosis	5(22.73%)	4(17.39%)	0.722
▪ Transient risk factors for venous thrombosis	12(54.55%)	14(60.87%)	0.668
▪ Permanent risk factors for venous thrombosis	14(63.64%)	9(39.13%)	0.140
▪ Two risk factors for venous thrombosis	10(45.45%)	7(30.43%)	0.299
▪ Three risk factors for venous thrombosis	1(4.55%)	1(4.35%)	1

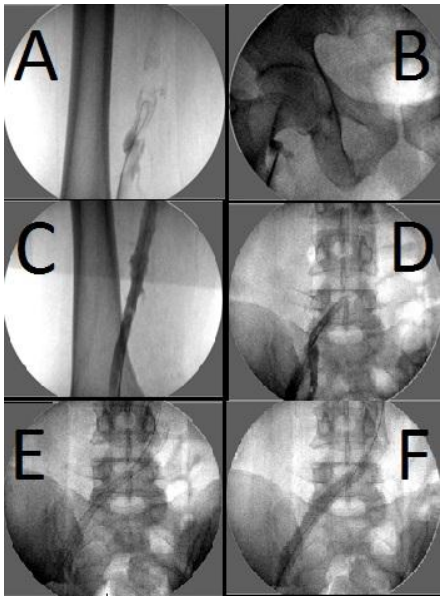

Figure (1):
A: Left iliofemoropopliteal segment loaded with thrombi
B: Partially occluded common femoral vein, totally occluded left-sided pelvic veins
C: Femoropopliteal segment cleared of thrombus load
D: Restored patency of pelvic veins
E: Wallstent (Boston Scientific, USA) 14mm×90 mm deployed in a stenosed left common iliac vein
F: Resumed normal flow in the iloocaval segment

Five clinically relevant non major bleeding complications were reported in the CDT group (22.73%), of which four bleeding incidents were procedure-related (18.18%). There was a single case (4.55%) of groin hematoma (contralateral; related to the puncture used for IVC filter (Denali® Vena Cava Filter, Bard, USA) placement in a patient with a free floating thrombus tail), two cases (9.91%) of popliteal fossa hematoma (related to the puncture sites), and a single case (4.55%) of gingival bleeding. All were managed conservatively and none had blood transfusion. The remaining patient (4.55%) developed menorrhagia with hemoglobin drop of 1 gm/dl in 4 days, related to anticoagulant therapy. This was managed conservatively. In the control group, two patients (8.70%) experienced bleeding complications. One patient (4.35%) had major upper GI bleeding (4 months following DVT, upper GI endoscopy revealed erosive gastritis and bulb duodenitis). The other patient (4.35%) had gynecological bleeding (menorrhagia, without hemoglobin drop, she was managed conservatively). None of the patients in the CDT group experienced allergic reactions nor contrast induced nephropathy (CIN).Two patients (9.09%) in the CDT group suffered pulmonary embolism. In the control group, one patient

(4.35%) had pulmonary embolism postrandomization. Neither of the patients had hemodynamic compromise. Nevertheless, PE had no effect on the conductance and subsequent follow-up in our study. IVC filter insertion was not routinely considered during CDT. Five cases (22.73%) were considered for filter insertion. This was because two patient developed PE, and three filters were used for fear of embolization in patients having free floating thrombus tail extending to the IVC. We used the Celect filter (Cook Medical Inc., USA) in 3 patients, and the Denali Vena Cava Filter (Bard, USA) in the remaining two patients. Two patients in the CDT group (9.09%), and a single patient in the control group (4.35%) suffered recurrent DVT.

Post-thrombotic changes as evidenced by ultrasound/doppler:

At one month, patency of the iliac vein segment was significantly higher in patients in the CDT group than in the control group, with an absolute gain in patency of 38.34% (95% CI: 10.02%–59.24%; P = 0.008). Femoral venous reflux was significantly less prevalent among patients in the CDT group as compared to controls (P=0.023). Other post-thrombotic changes were significantly less prevalent in the CDT group than in the control group **(table 3)**. At six months, patency of the iliac vein segment was significantly higher in patients in the CDT group than in the control group, with an absolute gain in patency of 29.84% (95 CI: 3.26%–51.46%; P = 0.027). Femoral venous reflux was significantly less prevalent among patients in the CDT group as compared to controls (P =0.016). Other post-thrombotic changes in the iliofemoral veins were less prevalent in the CDT group than in the control group, yet with no statistical significance **(table 4)**.

In our series, we found a statistically significant relation between the immediate lysis grade after CDT, and patency of treated venous segments at 6 months (p=0.0302) **(Table 5)**.

Table (3): Post-thrombotic changes as assessed by duplex examination at one month in both the CDT group and the control group

	Catheter-directed thrombolysis (n = 22) N (%)	***Standard treatment (n = 23)N (%)***	***P-value***
Iliac vein patency	18(81.82%)	10(43.48%)	0.008
Femoral venous Reflux	10(45.45%)	18(78.26%)	0.023
Other post-thrombotic changes			
Pelvic vein			
• Residual thrombi	7(31.82%)	17(73.91%)	0.005
• Wall thickening	7(31.82%)	18(78.26%)	0.002
Femoral vein			
• Sclerosed vein	12(54.55%)	16(69.57%)	0.299
• Residual thrombi	7(31.82%)	13(65.52%)	0.095
• Wall thickening	12(54.55%)	19(82.61%)	0.042
• No flow	2(9.09%)	3(13.04%)	1

Table (4): Post-thrombotic changes as assessed by duplex examination at six months in both the CDT group and the control group

	Catheter-directed thrombolysis (n = 22) N (%)	***Standard treatment (n = 23) N (%)***	***P-value***
Iliac vein patency	19(86.36%)	13(56.52%)	0.027
Femoral venous	12(54.55%)	20 (86.96%)	0.016
Reflux			
Other post-thrombotic changes			
Pelvic vein			
• Residual thrombi	5 (22.73%)	8 (34.78%)	0.372
• Wall thickening	8 (36.36%)	13 (56.52%)	0.175
Femoral vein			
• Sclerosed vein	11 (50.00%)	13 (56.52%)	0.661
• Residual thrombi	4 (18.18%)	3 (13.04%)	0.699
• Wall thickening	12 (54.55%)	15 (65.22%)	0.465
• No flow	1 (4.55%)	1 (4.35%)	1

Table (5): Relation between immediate thrombolysis grade and 6-months patency after CDT

	Iliac vein patency at 6 months N(%)	***P value***
Grade I lysis (n=1)	0	0.0302
Grade II lysis (n=6)	5(83.33%)	
Grade III lysis (n=15)	14(93.33%)	

Incidence and severity of PTS using the Villalta score:

During the follow-up period, 7 patients (31.82%; 95% CI12.36% to 51.28%) in the CDTgroup developed post-thrombotic syndrome, compared with 12 patients (52.17%; 95% CI31.76% to 72.58%) in the control group (p=0.167). The absolute risk reduction for post-thrombotic syndrome was 20.36%(95% CI -8%–44.53%), thus the number needed to treat to avoid one post-thrombotic syndrome was 5 (95% CI 2-12). Most patients with post-thrombotic syndrome in both groups presented with mild post-thrombotic syndrome **(table 6)**.

Table (6): Severity grading of PTS at 6-months using the Villalta score in each of the CDT group and the control group

	Catheter-directed thrombolysis (n=22)	***Standard treatment (n=23)***	***p value***	***Absolute risk Reduction***
Post-thrombotic syndrome	7(31.82%)	12(52.17%)	0.167	20.35%
Villalta severity category				
Mild (score 5–9)	5	9	1	---
Moderate (score 10–14)	2	2		
Severe (score >14)	0	1		

Severity grading of chronic venous disease using Venous Clinical Severity Score (VCSS):

During the follow-up period, the mean VCSS was 5.1±2.59 in the CDT group, while that in the control group it was 6.2±2.35. Although patients in the CDT group had a lower mean score, the difference was not statistically significant (p=0.081). VCSS indicates the severity of chronic venous disorders regardless the patient has or has not PTS. Moreover, there is no cut off value that distinctly represents the presence of PTS. Whereas, the Villalta score value of 5 indicates the presence of PTS. In an attempt to extend the applicability of the VCSS and to be able to draw a cut off score value from the VCSS indicative of the presence of PTS, Linear regression was done **(Table 7)**. Through applying the linear regression between the Villalta score of our patients and their VCSS score, an equation was generated.

Equation:-

$$VCSS = 2.954 + (0.740 \times Villalta).$$

Table (7): Linear regression to detect the VCSS using the Villalta score

Model		***Unstandardized Coefficients***		***Standardized Coefficients***	***T***	***P value***
		B	**Std. Error**	**Beta**		
VCS	**(Constant)**	***2.954***	***.231***		***12.795***	***<0.001***
S	**6m Villalta**	***.740***	***.053***	***.957***	***14.006***	***<0.001***

Equation:- $VCSS = 2.954 + (0.740 \times Villalta)$

It is entrenched that, a Villalta score of 5 indicates the presence of PTS, when we apply the equation, a Villalta score of 5 will be equivalent to VCSS of 6.654.

$VCSS = 2.954 + (0.740 \times 5) = 6.654$

By applying the same equation, we calculated that a Villalta score of 10 is equivalent to a VCSS of 10.354, and a Villalta score of 15 is equivalent to a VCSS of 14.054. Therefore, we proposed an *adjusted VCSS* for definition and grading of PTS, in which we can grade PTS into mild (VCSS of 7 to 9), moderate (VCSS of 10 to 13), and severe (VCSS ≥ 14).When applying this adjusted VCSS to our study population, we found that during the follow up period, 5 patients (22.73%) allocated additional CDT developed PTS, compared to 9 patients (39.13%) in the control group. The absolute risk reduction for post-thrombotic syndrome was 16.40%, thus the number needed to treat to avoid one post-thrombotic syndrome was 6. Most patients had mild PTS, while none of patients in either groups developed severe PTS **(table 8)**.

The difference between the Villalta score and the VCSS system regarding the rate of development of PTS in our study population was not statistically significant **(table 9)**.

Table (8): Severity grading of PTS at 6-months using the VCSS in each of the CDT group and the control group

	Catheter-directed thrombolysis (n=22)	***Standard treatment (n=23)***	***p value***	***Absolute risk Reduction***
Post-thrombotic syndrome	5(22.73%)	9(39.13%)	0.235	16.40%
VCSS category				
Mild (score 7–9)	3	8	1	---
Moderate (score 10–13)	2	1		
Severe (score ≥14)	0	0		

Table (9): Difference in PTS incidence using the Villalta score and the adjusted VCSS

	Using the Villalta score	*Using the adjusted VCSS*	*p value*
Catheter-directed thrombolysis (n=22)	7(31.82%)	5(22.73%)	0.498
Standard treatment (n=23)	12(52.17%)	9(39.13%)	0.365

DISCUSSION

In this prospective, randomized controlled trial, we have evaluated the efficiency of adding catheter directed thrombolysis to conventional anticoagulation; as compared to conventional anticoagulation alone; for treatment of patients with acute iliofemoral deep vein thrombosis. We included patients with proximal DVT (with involvement of the iliac venous segment), since thromboses in this location are associated with a high risk of post-thrombotic syndrome, thus these patientsare expected to gain the most benefit from our intervention.The CaVenT study [5-7] included a population similar to ours, except their upper age limit, which was 75 years, compared to 70 years in our study. It included patients with symptoms that had lasted for less than 21 days, compared to the 14 days in our study. Our study population was similar to that of Elsharawy and Elzayat [11], Manninen and colleagues [12], Bækgaard and colleagues [13], and Sillesen and colleagues [14]. Bækgaard and co-workers excluded patients with thrombosed popliteal and calf veins [13].

In the current study, 20% of patients had no identifiable risk factors for DVT. We did not screen patients with unprovoked DVT for inherited thrombophilia. Most of the laboratory tests required to diagnose thrombophilia were not readily available, and those available were time-consuming. Nevertheless, all patients with unidentifiable risk factors were considered for extended anticoagulant therapy.In the CaVenT trial, thrombophilia screening was performed in all patients before or after therapy, with vitamin K antagonist. Thrombophilia was found in 38% of CDTpatients, and in 34% of patients in the control group. Combined thrombophilia was encountered in 5% of patients in the CDT group, and in 2% of patients in the control group [5]. In the study of Sillesen et al, 67% of patients had thrombophilia, half of them had more than one factor [14].

In our study, access to the venous system was gained through the ipsilateral popliteal vein, with the patient in the prone position, and under sonographic guidance to avoid vein wall lacerations and inadvertent arterial puncture. It is often difficult to cross an occluded iliofemoral vein from the internal jugular vein or the contralateral common femoral vein, and venous valves may prevent safe catheterization. In the CaVenT trial, the popliteal vein was used preferentially, but the calf or inguinal veins were other options for venous access [15]. Several other studies used the ipsilateral popliteal vein as their access site, under sonographic guidance [11], [14], [13]. Lee and colleagues, 2013 used the ipsilateral popliteal or short saphenous veins as an access site under sonographic guidance [16]. Access sites in the study of Manninen et al. varied depending on the level and extent of thrombosis. Contralateral femoral vein access was used if an iliocaval segment was not involved in the thrombosis. Ipsilateral popliteal or proximal deep crural vein access was used in cases of thrombosis extending up to the proximal common iliac vein or inferior vena cava [12]. In the study of Semba and Dake, 1994, venous access was through the right internal jugular vein, common femoral vein, or popliteal vein with special preference of the right internal jugular vein [17]. Bækgaard and co-workers stipulated the presence of at least open distal half of popliteal vein to act as an access site for their intervention [13]. On the contrary, we found that a thrombosed popliteal vein was easier to puncture than a patent vein; a finding that might be explained by the fact that a thrombosed "distended" vein is relatively fixed in situ and not pushed away by the puncture needle.

A thrombolysis grade was calculated to define the efficacy of thrombolysis in each patient of the CTD group. This was the same method adopted in the CaVenT trial [15] as well as in the study of Mizuno et al 2015, [18]. This method could have high degree of bias. On the other hand, Elsharawy and Elzayat, 2002, assessed the degree of thrombus lysis by comparing the venous duplex performed prior to hospital discharge, and duplex on admission [11]. Other studies did not report a

specific method to assess their technical success [14], [13], [12].

Forteen patients (63.64%) treated by CDT had an underlying left iliac vein stenosis. They were treated by balloon angioplasty. Stenting of the lesion was performed in 11/14 patients (78.57%) with self-expanding Wallstents ®. In the study of Elsharawy and Elzayat, only one patient (out of 18; 5.56%) had an underlying left iliac vein lesion which was stented [11]. In the study of Sillesen et al., 30 of the 45 occluded veins (67%) revealed underlying stenoses in the iliac veins. Two of the stenotic lesions were on the right side. The remaining 28 were found on the left side. All were treated with balloon angioplasty and stenting (mainly Wallstent®, Boston Scientific, but also Memotherm®, Bard, and Smart® Stent, Cordis) [14]. In the CaVenT trial, 23 patients (out of 90; 25.56%) received balloon angioplasty, 15 patients (16.67%) received venous stents [6].

IVC filter insertion was not routinely considered during CDT. In the current study, five patients (22.73%) were considered for filter insertion. The indications for filter placement included the presence of a free floating thrombus tail extending to the IVC (in 3 patients), and the development of PE during the procedure (in two patients).

In our study, none of the patients in the CDT group experienced major bleeding complications, while a single patient in the control group had a major upper GI bleeding related to anticoagulant therapy. Further two patients (one in the CDT group, and one in the control group) had minor bleeding episodes related to anticoagulant therapy. Procedure related bleeding occurred in 4 patients (18.18%) in the CDT group, all were minor. Three out of those were puncture site-related. In the early results of the CaVenT trial; following recruitment of 103 patients; a total of 10 overt bleeding complications were reported in relation to the 49 CDT procedures (20.41%). Major complications were reported in two patients (4.08%). Two patients experienced bleeding complications related to anticoagulation (1.94%). [15]. In their late results, they excluded clinically irrelevant bleeding episodes. They reported a bleeding complication rate of 9%. Similar to our finding, they reported that most of the relevant bleeding events were related to the puncture site [6]. In the study of Sillesen et al, bleeding complications were observed in 16% of cases, however, it was severe only in 2.22% [14]. It is notable that no bleeding occurred in the Elsharawy and Elzayat study[11].

In our study, two patients (9.09%) in the CDT group, and one patient (4.35%) in the control group, had pulmonary embolism. This was in relation to the procedure in the two patients in the CDT group, and shortly following randomization in the patient in the control group. Nevertheless, PE had no effect on the conductance and subsequent follow-up in our study. Enden and colleagues in the early results of the CaVenT trial reported that no pulmonary embolizations or deaths occurred in relation to CDT [15].

Recurrent VTE was reported at our study in 2 patients (9.09%) in the CDT group, and in single patient (4.35%) in the control group. There was no statistically significant difference in the rate of recurrent thrombosis between the two treatment groups. In our study, we did not perform further interventions for those with recurrent DVT. In the CaVenT trial, 34 (19%) patients had a recurrent venous thrombosis, of whom six patients with chronic iliac vein occlusions received successful endovascularrecanalization with stenting. There was no statistically significant difference in the rate of recurrent thrombosis between the two treatment groups [5]. Based on our findings, as well as the findings of the CaVenT trial, it can be assumed that the addition of CDT to standard anticoagulant therapy does not appear to have an additional protection against recurrent thrombotic events.

Assessment of the treated venous segments by ultrasound / duplex studies had shown that patients treated with the addition of CDT had significant gain in iliac vein patency, and significantly less prevalence venous reflux than patients treated with anticoagulation alone, both at 1 month and at 6 months. Similar to our results, in the CaVenT trial, after a six month period of follow up, patency of the iliofemoral vein segment was found in 64.0% of patients in the CDT group and 35.8% of patients in the control group, corresponding to an absolute risk reduction of 28.2% (95% CI: 9.7%–46.7%; P = 0.004). Femoral venous insufficiency, as well as other post-thrombotic changes of the iliofemoral veins, did not differ significantly between the two treatment arms [15].

In our study, we found a statistically significant relation between the immediate lysis

grade after CDT, and patency of treated venous segments at 6 months (p=0.0302). On the contrary, the CaVenT trial did not find significant correlation between lysis grade and patency after 6 months. About 83% of patients with ineffective lysis (grade I) and 60% of the patients with effective lysis (grade II and III) had regained iliofemoral patency during the follow-up period [15].

A limitation in clinical studies on post-thrombotic syndrome is the absence of a gold standard for its diagnosis. Several scoring systems have been used for diagnosis and severity grading of chronic venous disorders. In the current study, we have used the Villalta score for diagnosis and severity grading of PTS.After a mean duration of follow-up of 10.78 months; 7 patients (31.82%) in the CDT group had a Villalta score ≥5. This was opposite to 12 patients (52.17%) in the control group. Though statistically insignificant (p=0.167), it was calculated that the absolute risk reduction for post-thrombotic syndrome was 20.36%, thus the number needed to treat to prevent one post-thrombotic syndrome was five.In the CaVenT trial, at six months, there was no difference in PTS as assessed with the Villalta scale between the two treatment groups. About 30% of patients in both treatment groups had a Villalta score of 5 or more, suggesting "persistent subacute post-thrombotic symptoms preceding a stable clinical phase when PTS can finally be assessed". After two-year follow-up period, the authors reported an absolute risk reduction; for PTS; of 14.4% and thus the number needed to prevent one PTS was 7 [6]. After five years, 43% of patients with catheter-directed thrombolysis developed post-thrombotic syndrome, compared with 71% in the control group (p<0 · 0001). The absolute risk reduction for post-thrombotic syndrome was 28%, thus the number needed to treat to avoid one post-thrombotic syndrome was 4 [5]. It appears that the effect of CDT on the reduction of the risk of development of PTS increases with time and with recruitment of more patients.

Although PTS is considered a chronic disorder, it was shown in the CaVenT trial that among patients with a Villalta score indicating post-thrombotic syndrome after 2 years, 12% had a score of less than five (i.e., no post-thrombotic syndrome) at the 5 year follow-up [5]. This could indicate a limited applicability of the scale over time. Also, it does not take account of the duration of symptoms, possible lower leg comorbidity, or symptoms typically observed in venous claudication. Another drawback of the Villalta scoring system is that 5/11 of the descriptors are related to the patients' perception of pain, cramps, heaviness, paresthesia, and pruritus. This rendered the scoring system more or less "subjective".

In the current study, we also used the VCSS for severity grading of chronic venous disease in both the CDT and the control groups. Although patients in the CDT group had a lower mean score, the difference was not statistically significant (p=0.081).The VCSS is more objective, since only one descriptor is related to patient perception of pain. However, VCSS indicates the severity of the venous problem regardless the patient has or has not PTS. The use of compression stocking can "inflate" the overall VCSS. Moreover, there is no cut off value that distinctly represents the presence of PTS. In order to maximize the benefit of the VCSS (being more objective), and to mitigate the drawbacks of the Villalta score (being more subjective), we proposed an *adjusted VCSS* for definition and grading of PTS, combining the benefits of both available scores (the Villalta score, and the VCSS). When we applied the *adjusted VCSS* on our study population, the incidence of PTS showed no statistically significant difference when we used either of the Villalta score or the *adjusted VCSS*. Therefore, the *adjusted VCSS* can be used confidently for the definition and grading of PTS. However, larger sample are needed for further confirmation of reliability of the proposed *adjusted VCSS*.

CONCLUSION

In the treatment of acute iliofemoral deep vein thrombosis, the addition of catheter-directed thrombolysis to standard anticoagulant therapy; when compared to standard anticoagulant therapy alone; is safe and tolerated by most of the patients. The addition of CDT resulted in significantly higher iliac vein patency, significantly less venous reflux, and 20% risk reduction for the development of post-thrombotic syndrome. Yet, it does not appear to have an additional protection against recurrent thrombotic events.

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