

Original Research Article

Anticoagulation alone versus combined catheter-directed thrombolysis and anticoagulation in treatment of acute ilio-femoral deep venous thrombosis

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ABSTRACT

Background: It was found that 50% of patients with iliofemoral deep venous thrombosis (DVT) treated by anticoagulant alone and compression stocking developed post thrombotic syndrome (PTS). Accelerated removal of thrombus by thrombolytic agents may increase venous patency and prevent PTS. The objective of the study was to assess short-term efficacy of additional catheter directed thrombolysis (CDT) compared with standard anticoagulant therapy alone.

Methods: Prospective, randomized, controlled study on 50 patients (18–75 years) with acute iliofemoral DVT and symptoms <21 days were randomized to receive additional CDT or standard anticoagulant therapy alone. After 6 months, vein patency and insufficiency (reflux) was assessed using duplex ultrasound by an investigator blinded to previous treatments.

Results: Fifty patients were allocated additional CDT (n=25) or ACs alone (n=25). After CDT, grade III (complete) lysis was achieved in 17 (68%) and grade II (50%–90%) lysis in 5 patients (20%). One patient suffered major bleeding and two had clinically relevant bleeding related to the CDT procedure. After 6 months, iliofemoral patency was found in 17 (68%) in the CDT group vs. 8 (32%) controls, corresponding to an absolute risk reduction 36% (95% CI, p=0.002). Femoral venous insufficiency was found to be higher among the ACs group 11 patients (44%) vs. 7 patients (28%) in the CDT group.

Conclusions: After 6 months, additional CDT increased iliofemoral patency from 32% to 68% and decreased venous insufficiency from 44% to 28%.

Keywords: Chronic venous disease, Catheter directed thrombolytic therapy, Acute deep venous thrombosis

INTRODUCTION

Deep venous thrombosis (DVT) is the third commonest cause of cardiovascular morbidity and mortality.¹ It occurs in 1/1000 population per year in the United States of America (USA).² Pulmonary embolism (PE) is the most serious early complication of acute DVT while post thrombotic syndrome (PTS) is the most common late complication of acute DVT, and is responsible for a

greater degree of chronic socioeconomic morbidity, and lower quality of life.^{3,4} PTS results from chronic venous hypertension due to persistent venous obstruction and/or venous insufficiency (reflux) after inflammatory destruction of venous valves in response to acute DVT.⁵ About 50% of patients with proximal ilio femoral DVT are associated with more severe acute symptoms and a higher risk to develop PTS inspite of anticoagulant therapy and compression stockings.⁶⁻⁸ Recurrent

thrombotic events appear to compete with early recanalization after acute DVT, increasing substantially the risk for developing PTS.⁹ Patients with proximal ilio-femoral DVT is highly associated with increased risk of recurrent venous thromboembolism than other types of DVT, increasing the severity of their post-thrombotic morbidity.^{7,10,11} Early removal of thrombus by thrombolytic agents may increase venous patency and prevent PTS.¹²

Systemic anticoagulation is the main line of management of VTE and it helps to prevent thrombus propagation, early and late recurrences, death from PE and long-term sequelae as the development of PTS and chronic pulmonary hypertension.¹³ 80% of patients with symptomatic DVT may have evidence of asymptomatic PE, and about 80% of patients with symptomatic PE have silent DVT.¹⁴

Patients with VTE should start anticoagulant therapy once the diagnosis is confirmed by duplex ultrasonography or when clinical suspicion is very high. Usually anticoagulation starts by rapid onset agents, heparins, and continues by vitamin K antagonists for 3- 6 months guided by INR between 2-3.¹⁵ Anticoagulant therapy depends on endogenous fibrinolytic activity to lyse the thrombus and recanalize the vein. If the lysis is complete, earlier venous patency is restored and valve function can be preserved, and vice versa.¹⁶ Patients who have complete thrombus lysis are less likely to develop recurrent DVT than those with persistent thrombus.¹⁷⁻¹⁹

The basic mechanism of thrombolysis is the activation of fibrin-bound plasminogen and resultant production of plasmin. The advantage of catheter directed thrombolysis technique is that the catheter delivers the plasminogen activator (PA) within the thrombus, which accelerates the lysis, decrease the dose of PAs compared to systemic dose, protect it from plasminogen activator inhibitor, and protect the active enzyme plasmin from neutralization by circulating antiplasmin with the advantage of being more effective and safer than systemic infusion of Pas.²⁰ Comparison of both treatment modality may provide a new guidelines to the use of CDT in iliofemoral DVT.

METHODS

A prospective randomized study carried out on 50 patients presented with acute lower limb iliofemoral DVT attending Menoufia University Hospital emergency department between August 2017 and August 2018 and followed up till February 2019. The patients were randomly categorized into two groups group A (25 patients) and group B (25 patients). Group A was treated by ACs alone and group B by CDT in addition to ACs. ACs were given according to international guidelines using low molecular weight heparine (LMWH) (Clexane) followed by oral warfarin for at least 6 months. This study was accepted and approved by ethical committee.

An informed written consent was taken from all the patients.

The patients with age ranged from 18-75 years, onset of symptoms less than 21 days and patients objectively verified DVT in the common iliac vein (CIV), or / and the external iliac vein (EIV) + common femoral vein (CFV) and the upper half of the thigh + distal femoral vein (FV) ± popliteal vein were included in the study while patients received anticoagulant therapy >7 days before trial, with contraindications to thrombolytic therapy such as renal impairment (creatinine clearance <30 ml min), pregnancy, recurrent ipsi-lateral DVT, malignancy requiring chemotherapy or patients indicated for thrombolytic therapy such as (phlegmasia alba or cerula dolens) or isolated vena cava thrombosis were excluded from the study.

LMWH (Clexane) was given to both treatment groups according to international guidelines for the first 7 days then VKAs (warfarin) (marivan) for at least the next 6 months. CDT was started on the next workday for group B patients. Meanwhile they received subcutaneous LMWH. Before the CDT procedure, LMWH was discontinued for at least 12h. All cases were operated in an angioset operating room with peripheral vascular capabilities under complete aseptic conditions using nonionic contrast medium (Ultravist, Bayer company, Germany), local anesthesia (lidocaine 5%) was applied to the site of puncture and a 6 French sheath introduced into popliteal vein with duplex ultrasound guidance, and if failed access through saphenous vein was done. Venography was performed through the sheath to determine the extent of the thrombus. We advance the wire and catheter above the proximal part of the thrombus and fitting-sized perfusion catheters (Fountain catheter; Merit Medical Systems, Inc., South Jordan, Utah, USA) 30 or 50 cm, were positioned. If the wire fail to pass, the procedure was terminated and the case was excluded from the study. Next, 20 mg of alteplase (Actilyse; Boehringer-Ingelheim, Ingelheim am Rhein, Germany) diluted in 500 mL 0.9% NaCl was infused at 0.01 mg /kg/1h with a maximal dose of 20 mg per 24 h and maximal duration of 96 hrs. Treatment is continued in intensive care unit for optimal monitoring of blood pressure and pulse and puncture site was inspected four times daily. Hemostasis was also monitored by daily analysis of hemoglobin, fibrinogen and platelet counts. Thrombolysis was assessed daily by venography using a contrast injection through the sheath and/or perfusion catheter. Each vein segment, that is, CIV, EIV, CFV, the proximal and distal FV and popliteal vein, were given a score, where 0 =open vein, 1 =partially occluded vein, and 2 =completely occluded vein. Total thrombus score before and after lysis was calculated by adding the segmental scores. The difference between the pre and post lysis thrombus scores divided by the pre-lysis score gave the grade of thrombolysis; grade I ≤50%; grade II =51%–90%, and grade III =complete recanalization. Veinoplasty ±stenting was done to dilate iliac vein if

there was a significant stenosis (>50%). During CDT, anticoagulants were discontinued. Overt bleeding and symptoms suspect of bleeding or PE were dealt with according to local routines. Major bleeding was classified if it was overt with a decrease of 2 g/dl hemoglobin, led to transfusion of 2 units packed red blood cells (PRBCs), was intracranial, retroperitoneal, or in a critical organ, or contributed to death. Clinically relevant non-major bleeding included, as intervention for epistaxis, a visible hematoma, or spontaneous macroscopic hematuria. All other hemorrhages were categorized as trivial. A weight-adjusted full therapeutic dose of subcutaneous LMWH was initiated 4hrs after the end of CDT. Then oral anticoagulation was established as described earlier according to guidelines. Immediately after CDT or on entering the trial, all patients received knee-high elastic compression stocking (ECS) class II and were advised daily wear for 24 months.

Assessment at 6 months follow-up

Short-term end-point evaluation by duplex ultrasound assessment of the veins of all patients in both treatment groups was performed after 6 months \pm 2 weeks by one radiologist, who was unaware of the patient's treatment allocation and medical history. No adjudication committee was present. The venous system was evaluated using duplex ultrasound. Gray-scale ultrasound was used for assessed compressibility of the femoral vein. Doppler ultrasound was used to evaluate ilio-femoral venous flow and femoral venous insufficiency (reflux). Insufficiency was evaluated in the standing position, and deep venous reflux was defined as reversal of the velocity curve lasting longer than 1 s after standardized distal pneumatic decompression.²² Patients having any of the following were categorized not having regained iliofemoral venous patency: partial or complete incompressibility of the femoral vein, no flow in pelvic or femoral vein. Patients with duplicate femoral veins with normal compressibility and flow in at least one course were considered successfully recanalized.

RESULTS

The control (anticoagulant therapy only) group (Group A)

The mean age of patients was 48 years ranging from 18 to 75 years. Male to female ratio was 2:3. Ten patients (40%) had right sided DVT while 15 patients (60%) had left sided DVT. Two patients (8%) had duplicated femoral vein by duplex u/s. Four patients (16%) had history of previous trauma (car accident) one month ago. Two patients (8%) had history of abdominal surgery 3 weeks ago in the form of surgical removal of renal stone. Seven patients (28%) were bed ridden due to old age and old cerebral stroke. Eight females (32%) were in the post-partum period. Two female patients (8%) had history of oral contraceptive pills. Two patients (8%) had positive history of first degree relative DVT.

Table 1: Main characteristics of the patients.

	Catheter-directed thrombolysis group (n=25)	Anticoagulation group (n=25)
	N (%)	N (%)
Age	Rang (18-72) mean 48 years	Range (20-81) 52 years
Sex		
Male	15 (60)	10 (40)
female	10 (40)	15 (60)
Side of DVT		
Right side	8 (32)	10 (40)
Left side	17 (68)	15 (60)
Duration of symptoms (days)	10-21	9-15
Duplicate femoral vein	3 (12)	2 (8)
History of previous surgery	1(4)	2 (8)
History of previous trauma	2 (8)	4(16)
Short term immobility (bed ridden patients)	5 (20)	7 (28)
DVT in puerperium	1 (4)	8 (32)
Oral contraceptive pills	2 (8)	2 (8)
Obesity	4 (16)	5 (20)
First degree relative with DVT	3 (12)	2 (8)
Factor V leiden	1 (4)	2 (8)
Protein S deficiency	1 (4)	0
Lupus anticoagulant	1 (4)	0

Table 2: Lysis grade according to duplex ultrasound.

	Grade I	Grade II	Grade III
	N (%)	N (%)	N (%)
Group A after 6 months	9 (36)	8 (32)	8 (32)
Group B after 6 months	3 (12)	5 (20)	17 (68)

Two patients (8%) had factor V deficiency while no patient had protein S deficiency or positive lupus anticoagulant as shown in Table 1. Nine patients (36%) had grade I lysis, 8 patients (32%) had grade II lysis and 8 patients (32%) had complete lysis (grade III) as shown in Table 2.

Pulmonary embolism (PE) occurred in two patients and managed by admission to CCU, monitoring and the two had a lifelong anticoagulation therapy on discharge. Two patients had epistaxis and gingival bleeding during

follow-up that was self-limited by modification of marevan dosage.

CDT group (group B)

The mean age of patients was 53 years ranging from 28 to 75 years. Male to female ratio was 3:2. Eight patients (32%) had right sided DVT while 17 patients (68%) had left sided DVT. Three patients (12%) had duplicated femoral vein by duplex u/s. Two patients (8%) had history of previous trauma (car accident) one month ago. One patient (4%) had history of abdominal surgery 2 weeks ago in the form of open cholecystectomy. Five patients (20%) were bed ridden due to old age and cerebral stroke. one female (4%) was in the post-partum period. Two female patients (8%) had history of oral contraceptive pills. Three patients (12%) had positive history of first degree relative DVT. Factor V deficiency was found in one patient (4%). One patient had protein S deficiency and one other patient had positive lupus anticoagulant as shown in Table 1.

Three patients (12%) had ineffective (grade I) lysis. Five patients (20%) achieved (grade II lysis), and complete lysis (grade III) was present in 17 patients (68%) as shown in Table 2.

Two of the three CDT procedures that resulted in grade I lysis were prematurely ended because of major bleeding that lead to decrease of heamoglobin more than 2 gm% at the puncture site. Among grade II lysis patients, two had increasing hematoma at the puncture site that required stopping the CDT with compression of the site with return to the CDT procedure later on after 10 days. Mean duration of CDT was 2.1 days. Balloon angioplasty and stenting of the iliac vein was performed in 4 patients.

Three patients were discovered to have cancer later on with initiation of chemotherapy and one of them had a lt hemicolectomy for cancer colon.

Hemostasis monitoring by daily analysis of hemoglobin, fibrinogen, INR and platelet count didn't reveal significant changes. Major complications (increasing hematoma) were reported in 2 patients; they required stopping the procedure and compression and we regained the procedure within 10 days later. Ten patients suffered clinically relevant non-major bleeding related to puncture site and managed by conservative measures. One patient suffered epistaxis lasting 3 hours with local measures applied as nasal pack. There were no PE nor deaths. Minor complications without clinical relevance occurred in 10 patients presenting by pain due to alteplase injection and treated by morphia injection.

Efficacy outcomes at 6 months

Patency of the ilio-femoral vein segment was regained in 17 (68%) patients in the CDT group and 8 patients (32%) in the control group, corresponding to an absolute risk

reduction of 36% (95% CI, p=0.002). Femoral venous insufficiency was found in 7 cases (28%) and 11 cases (44%) among CDT and the control group, respectively with absolute risk reduction being 16% (CI=95%, p=0.002). Among the 25 patients in the CDT group, lysis grade and the use of angioplasty/stent was correlated with 6-months patency, as the 4 patients with stenting done were still have patent iliofemoral segment at the six month follow up. All the patients with effective lysis (grade III) had regained iliofemoral patency. Venous obstruction as assessed by duplex venous flow by loss of phasicity and femoral incompressibility and other post-thrombotic changes of the iliofemoral veins, that is, wall thickening and echoic content of vein lumen was found in 8 patients (32%) in the CDT group and in 17 patients (68%) in the control group with absolute risk reduction of 36% (95% CI; p=0.002).

DISCUSSION

The main goals for treating the patients with acute DVT is to prevent the incidence of PE, restore the blood flow through the thrombosed venous segment, prevent recurrent thrombosis, and to preserve the venous valve function. This will minimize the morbidity and mortality of PE and diminish the sequelae of the post thrombotic syndrome.²² The severity of postthrombotic syndrome depends on both venous reflux and obstruction together, as opposed to reflux or obstruction alone. About two thirds of patients with acute iliofemoral DVT will develop edema and pain, and only 5% will develop ulcers inspite of adequate anticoagulation.²³

Our study aimed to evaluate relevant clinical effects of additional CDT in acute lower limb DVT, and we found that the additional CDT significantly increased the short term 6 months venous patency from 32% to 68% (p<0.002) as compared with standard anticoagulant treatment alone and use of Elastic Compression Stocking (ECS) and this matches with the study done by T. Eenden, el where additional CDT increased 6 months patency from 36% to 64% (p<0.004) as compared with standard anticoagulant treatment and use of ECS.²⁴ Also, there are 6 studies done by Watson and colleagues on thrombolysis for acute DVT indicated patency in 43% after thrombolytic therapy vs. 17% in the control group.²⁵

The study of Elsharawy and colleagues on 35 patients reported complete lysis in 72% after CDT vs. 12% in the control group compared to 68% in CDT and 32% in the control group in our study.²⁶

It was found, from the observational studies, that recurrent DVT of the limb is associated with increased risk of development of PTS in addition to other several factors such as thrombophilia, overweight and gender. Early recanalization of the vein is thought to preserve the valve function and prevent its destruction and development of PTS, but the relationship between early venous recanalization and long-term functional outcome

of the limb has yet to be documented.⁷ We found that CDT significantly reduced venous insufficiency that occurred in 28% in CDT group vs. 44% in the control group but these results did not match with that done in study by T. Enden, et al where venous insufficiency was not significantly reduced and occurred in 60% in the CDT group vs 66% in the control group but this may be due to smaller number of patients in our study.²⁵ This may indicate that if CDT reduces development of PTS, this is because of a reduction in obstruction and insufficiency. Our study allowed patients with history of DVT symptoms up to 21 days to be included compared with duration <10 days in other studies, however, mean duration of symptoms in patients receiving CDT was 6 days in both studies. Two episodes of major bleeding was seen related to the CDT procedure. Bleeding complications are usually related to puncture site of the vein and its incidence increases with repeated failed trials.

We perform venography initially to ensure the extent of thrombosis and compare with routine imaging with ultrasound. In conclusion, additional CDT not only significantly increased 6 months venous patency after iliofemoral DVT, from 36% to 64% but also, significantly reduced venous obstruction and venous insufficiency.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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