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Catheter Directed Thrombolysis in Treatment of Acute Iliofemoral Deep Venous Thrombosis: Determinants of Outcome

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ABSTRACT

Background: Acute deep vein thrombosis (DVT) of the lower limbs occurs in about 1.0 person per 1000 population per year and is associated with substantial morbidity. Although anticoagulation effectively prevents thrombus extension, pulmonary embolism, death, and recurrence may occur. Moreover, many patients develop venous dysfunction resulting in post-thrombotic syndrome (PTS). PTS is associated with reduced individual health-related quality of life and a substantially increased economic burden. Hence, additional and more aggressive treatment, including systemic thrombolysis, thrombectomy, and catheter- directed thrombolysis (CDT), has been introduced to accelerate thrombus removal. Numerous studies suggest that additional CDT may provide highly effective clot lysis. There is little doubt that the overall benefit of thrombolysis depends on multiple factors, including predisposing risks, symptom duration, thrombus extension, and technical approaches and interventional success. **Aim of the Work:** This study aimed to define predictors of immediate and mid-long-term anatomic and clinical failures to guide patient selection and to set a standard for patient and physician expectations. **Patients and Methods:** This is a prospective observational cohort study that enrolled 20 patients (22 limbs) who presented to the Ain Shams University hospitals in the period from 7/2015 to 7/2017 with acute iliofemoral deep venous thrombosis (IFDVT) and fulfilled the inclusion criteria (mentioned below). Intrathrombus catheter directed thrombolysis (CDT) was done. Assessments of predictors of immediate periprocedural success was based on degree of clot lysis and resolution of symptoms and signs. Incidence of postthrombotic syndrome (PTS) was calculated at 6 months postoperative using Villalta score (≥5 *vs* <5). **Results:** During the study duration, 20 patients (22 limbs) were recruited. The mean age was 40.95 ± 12.35 years old, 11 patients (12 limbs) were women. The indication for CDT was severe progressive pain/swelling (18 limbs), and phlegmasia cerulea dolens (4 limbs). 5 patients (7 limbs) had IVC thrombosis at the initial venography. 5 limbs had balloon dilatation only while iliac stenting was done in 12 limbs. 15 patients received CDT for 48 hours while 5 patients (7 limbs) received CDT for 24 hours (mean duration of CDT was 1.68 days). As regards bleeding, only 2 cases of those who had CDT for 24 hours had bleeding, while bleeding occurred in 12 cases of those who had CDT for 48 hours. There were no recurrent DVT, intra or postoperative pulmonary embolism nor death within the study population till the end of the follow up period (6months). 6 months post intervention, 7 limbs were free of PTS (Villalta score < 5), 15 limbs had mild to moderate PTS, and no patients had severe PTS. The mean Villalta score was 5.14 ± 1.859. **Conclusion:** In our study, determinants of outcome following CDT for acute IFDVT were: 1) access site, 2) dose of thrombolytic agent used, 3) duration of thrombolysis, and 4) thrombus score at the end of the procedure. More studies should be done comparing not only the effect of CDT on incidence of PTS but also its effect on its severity (e.g. Villalta score) on short and long term.

Keywords: Catheter directed thrombolysis, Iliofemoral, Deep Venous Thrombosis, Determinants, Outcome.

INTRODUCTION

Venous thromboembolism (VTE) is a major cause of morbidity and is the leading cause of death in hospitalized patients [(1)].

The complications of acute VTE, including DVT, pulmonary embolism (PE), and the postthrombotic syndrome (PTS), are the most common preventable cause of hospital death and a source of substantial long-term morbidity. Severe manifestations of the PTS are a consequence of ambulatory venous hypertension, which is determined by a combination of factors, including valvular reflux, persistent venous obstruction, and the anatomic distribution of these abnormalities [(2)].

Early aggressive treatment of acute iliofemoral DVT (IFDVT) is indicated to prevent chronic venous insufficiency [(3)]. Patients with IFDVT stand to benefit from a treatment strategy that removes the clot, such as catheter - directed thrombolysis (CDT) or venous thrombectomy, followed by effective anticoagulation [(1)]. Catheter-directed lysis seems to have a better outcome compared to anticoagulant treatment or systemic lysis [(4)]. There is little doubt that the overall benefit of thrombolysis depends on multiple factors, including predisposing risks, symptom duration, thrombus extension, and technical approaches and interventional success. The identification of patients who will achieve favorable outcomes and derive long-term benefits from intervention is therefore paramount [(5)].

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AIM OF THE WORK

This study is performed to identify potential markers for early and long-term efficacy of CDT and adverse events.

PATIENTS AND METHODS

The study protocol was reviewed and approved by Research Ethics Committee at Faculty of Medicine, Ain Shams University.

Study Design: Prospective Observational cohort study.

Study population: Patients presenting to ASU hospitals with Acute IFDVT, and fulfilling the inclusion criteria.

Sampling: The group size was determined by the study duration i.e. the study was planned to be carried out over 2 years, which meant that about 20 patients should be recruited during this period based on previous experience from previous years.

Inclusion criteria: All patients that will be enrolled in this study will fulfill the following inclusion criteria:

1) Symptomatic patients with IFDVT of ≤ 14 days duration, 2) First time IFDVT of the ipsilateral limb, 3) Age ≥ 18 and ≤ 65 years old, 4) Physically active patients, and 5) No contraindication to thrombolysis (conditions that are likely to be associated with existing or very recent hemorrhage):

(1) Active internal bleeding; (2) Recent (within 2 months) cerebrovascular accident, trauma, or intracranial or intraspinal surgery; (3) Known intracranial neoplasm; (4) Severe uncontrollable hypertension; (5) uncontrollable clotting disorders; (6) previous severe allergic reactions to the thrombolytic agent. (7) recent (within 10 days) operative or obstetric procedures, biopsy or procedure in a location that is not compressible, gastrointestinal bleeding, or trauma, including cardiopulmonary resuscitation; (8) left heart thrombus; (9) subacute bacterial endocarditis; (10) severe liver or kidney disease; (11) diabetic hemorrhagic retinopathy; (12) acute pancreatitis; (13) pregnancy; (14) any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location. 6) Informed signed consent by the patient to participate in the study.

Exclusion Criteria: Exclusion criteria included: 1) asymptomatic patients, 2) patients with isolated Infrainguimal DVT, 3) Patients presenting with symptoms >14 days, 4) age < 18 years or > 65 years, 5) bed ridden patients, 6) patients presenting with recurrent DVT in the ipsilateral limb, 7) patients with absolute and relative contraindications to CDT as mentioned above.

Preoperative evaluation: 20 patients were recruited were recruited, aging 19-64 years, 11 patients were women and 9 were men. Demographic and medical data were gathered from patients including age, habits of medical importance, medical history and family history. All patients had duplex scanning of the deep venous system of the affected limb(s) to appreciate the extent of thrombosis and to assess the access site. Regular Lab investigations were done including full blood count, kidney function tests, Liver function tests, and coagulation profile. Patients were administered therapeutic dose LMWH on admission.

Technique: Ultrasound-guided popliteal or short saphenous vein access was used (prone position) regardless of whether the clot involved the popliteal/tibial veins or not. We used 6F sheath in 20 limbs and 8F sheath in 2 limbs. Ascending venography was then performed through the sheath to determine the extent of the thrombus.

A 50 centimeter, 4 or 5 F multiple side-hole infusion catheter was positioned in the iliofemoral segment. An initial bolus (10-15 mg) of Recombinant Tissue Plasminogen Activator (rtPA / alteplase) was delivered in the interventional suite (or in operating room under mobile C-Arm imaging) via pulse spray technique. Patient was then transferred to ICU or High Dependency Unit and continuous infusion for 24 hours was initiated. Total dose of rtPA was 50 mg/24 hours.

Intraoperative Venography was done after 24 hours. If there is residual thrombosis, the patient was maintained on alteplase for further 24 hours, with maximum total dose of alteplase being 100 mg. Iliac vein stenosis seen on completion venography at the end of thrombolysis was treated with balloon dilatation with or without stenting according to the degree of residual stenosis and available equipment. All stents used were self-expandable Zilver Vena or Wallstents.

During the procedure patients were maintained on unfractionated heparin administered through the sheath with aPTT 1.5 times normal.

After the procedure, patients were maintained on LMWH. LMWH was then replaced with Warfarin. Patients who had stenting, also received clopidogril 75 mg/day. Anticoagulation and antiplatelets were continued for a minimum duration of 6 months postoperative. All patients were advised to wear above knee graduated elastic stockings for 2 years.

Endpoints were clearance of the thrombus load in the iliac segment, evident improvement of symptoms and signs, lysis for 48 hours, total failure of lysis after the first 24 hours, haemorhage threatening general condition of the patient and occurrence of pulmonary embolism.

The rate of clot lysis was estimated on the basis of the amount of residual clot at the completion venogram compared with the pretreatment venogram. A total thrombus score was calculated before, during, and at the completion of CDT by adding the scores for the following seven vein segments: inferior vena cava, common iliac vein, external iliac vein, common femoral vein, proximal and distal segments of femoral vein, and popliteal vein. Scores were 0 when the vein was patent and completely free of thrombus, 1 in case of a partially occluded vein, and 2 in case of a completely occluded vein, i.e., vein lumen totally filled with thrombotic material. Each segment was given a score, resulting in possible total thrombus scores of 0–14. In patients with bilateral DVT, each limb was calculated individually including the IVC segment, i.e. each limb still has possible score of 0-14.

The immediate efficacy of CDT was defined based on postlysis thrombus score and clot lysis grade at the end of the procedure. Lysis grade was calculated by dividing the difference of the total pre-and postlysis thrombus scores by the prelysis score, resulting in a grade III indicating 100% lysis with no residual clots, a grade II indicating 50%–99% lysis, and a grade I indicating less than 50% lysis. Lysis grades II and III (i.e., ≥ 50%) were considered successful outcomes.

The safety outcomes included complications related to thrombolysis during or shortly after the CDT procedure. Bleeding complications were categorized as major if they led to a hemoglobin decrease of at least 2 g/dL; required transfusion of at least 2 U of packed red blood cells; were retroperitoneal, intracranial, or in a critical organ; or contributed to death. Clinically relevant non major bleeding included, for example, intervention for epistaxis, a visible large hematoma, or spontaneous macroscopic hematuria. All other hemorrhages were categorized as trivial.

Follow up: Patients had follow up with clinical examination at intervals of 1, 3 and 6 months. PTS was diagnosed after 6 months based on the Villalta scale, with assessment of five patient-rated venous symptoms (pain, cramps, heaviness, paresthesia and pruritus) and six clinician-rated physical signs (pretibial oedema, skin induration, hyperpigmentation, pain during calf compression, venous ectasia and redness). Each sign or symptom is rated as 0 (none), 1 (mild), 2 (moderate), or 3 (severe), and summed to produce a total score.

A total score of less than 5 indicates no PTS, of 5–14 indicates mild or moderate PTS, and of 15 or more (or presence of venous ulcer) indicates severe PTS. Reporting of recurrent DVT or pulmonary embolism at the follow-up visits was confirmed by lower limb venous duplex and/or CT pulmonary angiography.

Statistical Analysis

Data were analyzed using SPSS© Statistics version 24 (SPSS© Corp., Armonk, NY, USA). Descriptive statistics were used to demonstrate patients' demographics, preoperative, intraoperative, and postoperative findings. Normally distributed numeric data were presented as mean and standard deviation. Categorical variables were presented as number and percentage. P-value is considered statistically significant if <0.05.

RESULTS

During the study duration, 20 patients (22 limbs) were recruited. The mean age was 40.95 (19-64) years, 11 patients (12 limbs) were women. The indication for CDT was severe progressive pain/swelling (18 limbs), and phlegmasia cereula dolens (4 limbs).

Table (1): Baseline characteristics of study cohort

		Mean	**SD**	**Minimum**	**mum**
Age		40.95	12.35	19	4
Weight		86.55	15.44	68	15
Demographics				**Number**	**cent**
Gender	Female			12	.5
	Male			10	.5
Affected Side	Right			9	.9
	Left			13	.1
Duration of symptoms	Less than 7 days			12	.5
	7-14 days			10	.5
Preop. Pulmonary embolism				1	.5

Caval involvement was present in 5 patients, 2 of them had bilateral iliocaval DVT due to IVC hypoplasia (one of them had bilateral phlegmasia cereula dolens). The popliteal segment was free from thrombosis in both patients. One patient had symptoms of pulmonary embolism before the intervention. He had an IVC filter inserted before the CDT. One patient had GA during the first visit to OR due to anxiety during sheath insertion.

Table (2): Angiographic findings

Angiographic findings		**mber**	**Percent**
IVC	Patent, completely free	15	68.2
	Partially occluded	2	9.1
	Completely occluded	5	22.7
CIV	Thrombosed	22	100
EIV	Thrombosed	22	100.0
CFV	**Thrombosed**	**20**	**90.9**
SFV	Thrombosed	20	90.9
Popliteal vein (Zone I)	Thrombosed	15	68.2
Long Saphenous vein (above knee)	Patent	8	36.4

All patients received 10-15 mg alteplase as bolus dose after catheter placement, and 35-40 mg given as infusion over 24 hrs. Total dose did not exceed 50 mg/24 hrs for a maximum of 48 hours.

Table (3): Immediate results of thrombolysis

	Mean	**SD**	**Minimum**	**Maximum**
Maintenance dose in mg	34.91	14.506	18	90
Initial Thrombus score	11.05	1.290	8	13
Thrombus Score after 24 hours	3.86	1.833	1	7
Degree of lysis in first 24 hours	64.82%	17.056%	36%	91%
Thrombus Score after 48 hours	1.64	1.432	0	4
Degree of lysis after 48 hours	78.73%	8.72%	64%	92%

5 patients (7 limbs) had IVC thrombosis at the initial venography. After 24 hours of lysis, the mean degree of lysis was 70.86%, compared to 62% in limbs without caval involvement.

In 10 patients (12 limbs) who had CDT within one week of appearance of symptoms, the mean lysis degree at the end of procedure was 75.83%. The other 10 patients who received CDT within 7-14 days of appearance of symptoms had mean lysis degree at the end of procedure75.9%.

5 limbs had balloon dilatation only while iliac stenting was done in 12 limbs; 9 limbs had one stent, while 3 limbs had 2 stents. All interventions were done to the iliac segment. No dilatation / stenting was done to IVC or femoropopliteal segment.

Bleeding complications occurred in 14 limbs. No surgical intervention was required for any of them. No recurrent DVT, PE or death occurred at the end of the follow up period.

15 patients received CDT for 48 hours while 5 patients (7 limbs) received CDT for 24 hours (mean duration of CDT was 1.68 days). There is a sharp increase in the degree of lysis in the first 24 hours, followed by a much slower increase in lysis. As regards bleeding, only 2 cases of those who had CDT for 24 hours had bleeding, while bleeding occurred in 12 cases of those who had CDT for 48 hours. This denotes less lysis and more bleeding in the second 24 hours.

Short Saphenous Vein was used for access in 5 limbs, while popliteal vein (zone II) was used in 17 limbs.

There were no recurrent DVT, intra or postoperative pulmonary embolism nor death within the study population till the end of the follow up period (6months).

6 months post intervention, 7 patients were free of PTS (Villalta score < 5), 15 patients had mild to moderate PTS, and no patients had severe

PTS. The mean Villalta score was 5.14 (SD 1.859), the minimum score was 1, and the maximum was 8.

10 patients (12 limbs) had CDT within one week of appearance of symptoms, 6 of them (8 limbs) had PTS at 6 months. 10 patients had CDT within 7-14 days of appearance of symptoms, 7 of them had PTS at 6 months.

No significant relation was found between the thrombus score at the start of procedure nor the degree of thrombus lysis at the end of the procedure and PTS at 6 months. However, higher thrombus score at the end of procedure was associated with higher incidence of PTS at 6 months.

Table (4): Comparing mean thrombus scores and degree of lysis with PTS

	Post Thrombotic Syndrome	N	Mean	Std. Deviation	P-value*	F-value	Significance
Degree of thrombus lysis after 48 hours	No Yes	7 15	71.69 73.54	48.353 45.417	1.115	0.2	NS
Initial Thrombus Score	No Yes	7 15	11.57 10.80	1.512 1.146	0.402	0.734	NS
Degree of thrombus lysis after 24 hours	No Yes	7 15	62.57 65.87	15.054 18.318	0.487	0.5	NS
Final Thrombus Score	No	7 15	1.86 2.53	.900 1.642	0.03	11.33	S

*p-value calculated using t-test

No significant association was found between IVC thrombosis and Villalta score at 6 months. Patients with caval involvement had mean score 5.43 at 6 months, while patients with non caval involvement had mean score 5.

12 limbs had iliac stenting, 7 of them had PTS AT 6 months (58.3%), and 5 limbs were free (41.7%). There was no significant association between iliac stenting and PTS at 6 months.

DISCUSSION:

Thrombolysis for symptomatic IFDVT can achieve relatively high rates of immediate thrombus clearance and reduce long term PTS morbidity, yet a considerable proportion of patients sustain bleeding complications, especially those who received higher doses of thrombolytic agent.

Immediate success rates vary in the current literature. This variability can be attributed in part to the heterogeneous patient population (baseline risk factors, clinical presentation, and anatomy of the DVT) and technical factors (CDT versus PMT, use of stents, and duration of lysis).

In our study, we followed the commonly used regimen in ASU hospitals as regard actilyse infusion; (10 – 15 mg bolus followed by infusion at rate 1.5 - 2 mg/hr not to exceed 50 mg rtPA in 24 hrs) which is the maximum dose according to published literature [(1)]. This is different from the dose used in the CaVenT and ATTRACT trials that used dose of 0.01 mg/kg/hr not to exceed 1.0 mg/hr of actilyse continuous infusion [(6)].

100% of our patients had thrombus lysis > 50%, compared to 88.8% of patients in the CaVenT study [(7)]. This may be due to higher doses of thrombolytic agent used.

We didn't find significant difference between patients presenting <7 days or 7-14 days as regards the final lysis grade or severity of PTS after 6 months. Unfortunately, we found no studies that reveal the effect of early (< 7 days) vs late (7-14) CDT on PTS at 6 months.

15 limbs received CDT for 48 hrs while 7 limbs received CDT for 24 hrs (mean duration of CDT was 1.68 days, SD 0.48). This duration is shorter than that used in the CaVenT trial (2.4 days), and this may be the reason why the incidence of PTS at 6 months in CaVenT is lower than ours (30.3% and 68% respectively) [(7)].

None of our patients had score ≥ 10 nor venous ulcer. Unfortunately, there is no data published as regard the Villalta score at 6 months for patients of CaVenT trial, however, 18 % of patients who received CDT/PMT in the ATTRACT study had severe PTS (Villalta score ≥10 or any score with venous ulcer) [(8)]. This finding might also be related to the fact that we used the maximum dose of actilyse (2 mg/hr).

Thus, the dose of thrombolytic agent used may play a more significant role than the duration of symptoms.

Caval involvement was associated with degree of lysis at 24 hrs and Villalta score similar to non caval involvement, thus we found no appreciated benefit from further thrombolysis more than 24 hours in patients with caval involvement. CaVenT and ATTRACT studies did not give subgroup analysis as regards caval thrombosis. However, a study was published in 2016 by Avgerinos et al about the effect of IVC thrombosis on success of thrombolysis and PTS. The authors found that IVC thrombosis does not have an impact on the technical success of thrombolysis in patients with iliofemoral DVT and that Caval thrombosis may not affect primary patency but is associated with a lower incidence of PTS after successful lysis [(9)].

No correlation was found between the lysis grade and patency or PTS. Lysis grade is a measure of percentage resolution of thrombus, and is not necessarily a good measure of residual thrombus. However, the thrombus score at the completion of CDT is a direct measure of residual thrombotic burden, which we believe may explain the correlation with PTS at 6 months.

When bleeding events without clinical relevance were excluded, our bleeding complication rate reached 50%, which is higher than many other studies; e.g. 9 % in the CaVenT study [(7)]. This may be attributed to the higher dose of thrombolytic agent used. Few studies compared between different access sites and bleeding complications, and no data was shown regarding effect of access site on incidence of access site bleeding in the ATTRACT nor CaVenT studies. However, a study published by Duan and Ni in 2016 compared bleeding complication with three access sites; SSV, GSV, and popliteal vein. Of the three routes tested, the SSV route was associated with more frequent complications. GSV catheterization was more effective because of its lower complication rate. Rate of complications with popliteal vein was less than SSV and more than GSV [(10)]. In our study we didn't use GSV for access. Access through the SSV had lower rate of clinically relevant non-major bleeding complications than popliteal vein (20% for SSV access, and 35.3% for popliteal vein).

We found no significant association between predisposing risk factors and the degree of lysis or severity of PTS. In their study about predictors of failure of CDT in IFDVT, Avgerinos et al concluded that recent surgery, male gender, phlegmasia, and malignant disease as predictors of immediate or long-term failure of thrombolysis for IFDVT [(5)]. The ATTRACT trial found that patients 65 years of age or older were less likely to benefit from pharmacomechanical thrombolysis than younger patients regarding development of PTS at 24 months [(8)].

The ATTRACT trial documented 2 recurrent VTE in 10 days, 1 fatal PE at 6 months, and no deaths at 10 days [(8)]. No recurrent VTE, post-lysis PE, or deaths occurred in our study. These may be due to the small number of participants.

Due to the very low compliance for performing the follow up duplex examination, no reliable data could be concluded from our study about the venous patency.

The only factor that had a significant relation to severity of PTS was the thrombus score at the end of the procedure. Higher final thrombus score was associated with higher Villalta score at 6 months.

Our trial had several limitations. There was a substantial number of missing assessments of the post-thrombotic syndrome. As expected, there were occasional missed visits among patients who returned for follow-up. The follow-up duration was not sufficient for the development of PTS in its full picture. There was a high rate of compliance as regard postoperative anticoagulation. However less than two thirds of the patients adhered to the use of elastic stockings as instructed by the treating physician. Finally, most patients received warfarin; although direct oral anticoagulants are now frequently used, this change did not affect the rates of the post-thrombotic syndrome, since both types of anticoagulation are similarly effective at preventing recurrent deep vein thrombosis.

CONCLUSION

In conclusion, we suggest that use of CDT/PCDT should be limited to patients with acute iliofemoral DVT, low projected bleeding risk, and either a) acute limb threatening circulatory compromise from DVT; or b) severe/worsening ongoing symptoms, documented major thrombus progression, or signs of impending limb threat despite initial anticoagulation.

Access through Short Saphenous vein is safer than popliteal vein, higher doses of thrombolytic agent should be avoided. Thrombolysis more than 24 hours is associated with higher bleeding complications, and caval involvement is not an indication for prolonged thrombolysis. Higher thrombus score at the end of the procedure is more accurate than degree of lysis in predicting occurrence PTS. Clinical screening for PTS using Villalta scale is a reliable and easy to perform tool, and avoids the noncompliance of patients in performing duplex studies. In our study, determinants of outcome following CDT for acute IFDVT were: 1) access site, 2) dose of thrombolytic agent used, 3) duration of thrombolysis and 4) thrombus score at the end of the procedure.

Finally, more studies should be done comparing not only the effect of CDT on incidence of PTS but also its effect on its severity (e.g. Villalta score) on short and long term.

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