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Editor's Choice – Factors Associated with Long-Term Outcome in 191 Patients with Ilio-Femoral DVT Treated With Catheter-Directed Thrombolysis

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WHAT THIS PAPER ADDS

The present study demonstrates, for the first time, that outcome in terms of competent veins after catheter-directed thrombolysis in ilio-femoral deep venous thrombosis is better in patients with symptom duration <14 days compared with patients with longer symptom duration.

Objective: To identify factors associated with long-term treatment success after catheter-directed thrombolysis (CDT) for acute deep venous thrombosis (DVT) involving the ilio-femoral vein.

Material and methods: This was a non-randomised observational cohort study. From 1999 to 2013, 191 consecutive patients (203 limbs) attending a tertiary vascular centre at Gentofte University Hospital, Denmark underwent CDT. All patients had ultrasonically verified acute ilio-femoral DVT with open distal popliteal vein and calf veins. Patients were seen in the outpatient clinic 6 weeks, 3, 6, and 12 months, and annually thereafter following the DVT. Successful outcome was defined as patent deep veins without reflux on Duplex ultrasound scanning (DUS). Data were collected prospectively as per protocol and analysed retrospectively.

Results: Median age was 27 years (range 14–74 years) and overall median lysis time was 56 h (range 22–146 h). A stent was placed in 106 limbs (52%). Six patients had major bleeding. The median follow-up was 5 years (range 1 month–14.3 years). The cumulative rate of patients with deep patent veins without reflux at 7 years was 79%. Multivariate Cox regression analyses showed that symptom duration >2 weeks (hazard ratio (HR) 2.78, 95% CI 1.14–6.73) and chronic post-thrombotic lesions (HR 19.3, 95% CI 7.29–51.2) were significantly associated with poorer outcome, while the pulse-spray technique (HR 0.15, 95% CI 0.05–0.48) was associated with better outcome. Age, gender, side, IVC atresia, stenting, and lysis duration did not affect outcome.

Conclusion: In this observational study of CDT for ilio-femoral DVT it was demonstrated that symptom duration less than 2 weeks, absence of chronic post-thrombotic lesions and use of the pulse-spray technique for CDT resulted in better primary patency including normal valve function in the long term.

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INTRODUCTION

Patients suffering from acute deep venous thrombosis (DVT) with involvement of the ilio-femoral vein segment have the worst outcome in terms of post-thrombotic syndrome (PTS) and Quality of life (QoL) if treated with anticoagulation (AC) only.[1,2] An ilio-femoral DVT involves the iliac and the common femoral veins with or without involvement of any additional vein segment.[3,4] The venous return from the femoral and/or the deep femoral vein is significantly impaired because of the poor rate of recanalisation and poor collateral development in the pelvic region. The thrombus may involve vein segments central and peripheral to the ilio-femoral vein.

Over the years, different methods for thrombus removal have been introduced to restore patency, save valve function, and reduce the occurrence of PTS. CDT has been practiced for the last 20 years and is considered to be a minimally invasive procedure.[4–7] A meta-analysis based on four studies comparing anticoagulation and CDT found a statistically significant reduction in the risk of venous obstruction (RR 0.38; 95% CI 0.18–0.37; $I^2 = 46\%$), PTS (RR 0.19; 95% CI 0.07–0.48; $I^2 = 64\%$) and a trend for reduction

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in the risk of venous reflux (RR 0.39; 95% CI 0.16—1.00; $I^2 = 92\%$) in patients who had CDT.[8] The Norwegian RCT (CaVenT study) including 176 patients demonstrated a 28% absolute risk reduction in PTS after 5 years as the most important result.[9]

During the last 16 years, the Vascular Clinic at Gentofte University Hospital, Denmark has offered CDT for patients with acute ilio-femoral DVT as part of a treatment algorithm. Data on safety, long-term patency results, valve function, PTS, and QoL based on this cohort, have been reported previously.[7,10—12] The cohort now contains a substantially larger number of patients, followed for a considerably longer time. The aim of this study was to identify factors associated with long-term treatment success using multivariate analysis.

MATERIAL AND METHODS

From 1999 to 2013, patients with acute ilio-femoral DVT were selected for CDT at the Vascular Clinic, Gentofte University Hospital, Denmark. Patients were referred from all regions of Denmark until 2010, when a second centre was established in the western part of the country. Inclusion criteria per protocol were first episode of ilio-femoral DVT, open distal popliteal vein and open calf veins, age <60 years for the first 60 patients and age <75 years thereafter, and symptom duration (assumed to be the best estimate of thrombus age) <14 days. During the study period a number of patients with symptom duration >14 days were also included. Exclusion criteria were previous ipsilateral DVT, pregnancy, malignancy, or other concomitant chronic or potentially life threatening disease, bleeding disorders, uncontrolled hypertension, recent surgery, and childbirth within the past week.[10] Approximately one in three patients referred for CDT were eligible. The remaining two thirds of the patients received anticoagulation according to national standards. This is in accordance with the findings of a recently published paper showing, that one third of patients with ilio-femoral DVT have open popliteal veins.[13]

Study design

The study prospectively included consecutive patients with ilio-femoral DVT referred to the Vascular Clinic at Gentofte University Hospital, who met the inclusion criteria per protocol. Medical records were reviewed for additional clinical data when necessary and at follow-up in 2014. No ethical approval was needed. Fifty predefined variables were kept on each patient in a local database of which 17 covariates (gender, age, side, stenting, number of stents, caval atresia, caval filter, caval extension of thrombus, thrombus extension below the inguinal ligament, treatment duration, use of pulse-spray, coagulopathy, child birth after initial thrombosis, use of low molecular weight heparin [LMWH] or heparin, symptoms >2 weeks, lifelong anticoagulation, underlying chronic post-thrombotic lesions) were selected. These 17 covariates were chosen as they were considered to be clinically or technically most relevant, and with a possible association with the outcome.

All patients were tested for thrombophilia (factor V Leiden mutation, prothrombin mutation 20210, protein C, protein S, antithrombin, plasminogen, anticardiolipin antibodies, lupus anticoagulant, and homocysteine).

Outcome as a surrogate marker for later PTS was defined as competent deep veins, defined as fully patent veins without evidence of reflux on duplex ultrasound scanning (DUS). Fully patent veins are compressible without any luminal echogenic appearance and with a normal flow pattern. A patent stent is characterised by no in-stent echoes, with a phasic flow pattern, and without any change in the colour mapping in the stent or in close proximity to it. Patency, in this context, is defined as an 85—90% open structure because DUS is unable to detect stenosis less than 10—15% in the vein or in the stent.

The CDT method

The distal popliteal vein was punctured under local anaesthesia using DUS guidance. A multiple side hole catheter with tip occlusion was placed in the thrombus. A bolus of 10 mg rtPA followed by rtPA 1.2 mg in 120 ml saline/h was administered using continuous infusion for the first 55 cases and thereafter using the pulse-spray infusion technique. In the first 129 patients, heparin was adjusted according to APTT (80—100 s). The following 62 patients had rtPA 1.2 mg/h mixed with LMWH adjusted by weight. All patients were treated with an intermittent pneumatic compression pump (IPC) during hospitalisation, and afterwards with a below knee class II graduated compression stocking (23—32 mmHg) and anticoagulation for at least 1 year. Radiological disappearance of thrombus in daily venograms accompanied by a decrease in D-dimer to values less than 10 mg/L was used as a marker for treatment success and determined the duration of lysis. Any remaining iliac obstruction (>10—15%) caused either by compression or in some cases by residual non-resolved thrombus material was stented. Venograms showing impenetrable occlusion, irregular and thickened vein walls, collaterals, and decreased flow were considered to be chronic post-thrombotic lesions.

Follow-up

All patients were seen in the outpatient clinic after 6 weeks, 3, 6, and 12 months, and annually thereafter. DUS was performed with the patient standing for assessment of valve function and in the supine position for assessment of vein (and stent) patency, as defined above. Femoral and popliteal vein reflux was defined as retrograde flow, following release of calf muscle compression, lasting more than 0.5 s, and in the common femoral vein lasting more than 1 s.

Statistical analyses

Continuous and interval variables are reported as median values with range. Per-protocol and intention-to-treat analyses were done. Associations between single variables and

outcome were tested in three steps. The first step was to test outcome at follow-up for each of the 17 variables with univariate non-parametric chi-square test. Based on this, three variables were excluded (number of stents, caval filter, and childbirth) because of absence of any correlation with outcome. In step 2, univariate time dependent survival statistics (Kaplan-Meier analyses with log rank-test) were performed. After this test, an additional three variables were excluded (caval thrombus, infra-inguinal thrombus, and lifelong anticoagulation), the first two because of poor correlation with outcome, the last as it was tied to the indication for treatment being either coagulation defect or chronic post-thrombotic lesion. In step 3, the remaining 11 variables were included in a multivariate time dependent Cox proportional hazard model (Table 1). The statistical software Stata version 10 (StataCorp LP, Texas, USA) was used, p values $<.05$ were considered to be significant.

RESULTS

A total of 191 patients (203 limbs) with ilio-femoral DVT underwent CDT between 1999 and 2013. Median follow-up was 5 years (range 1 month−14.3 years). The median age was 27 years (range 14−74 years), male/female ratio 53/138, and left/right ratio 146/57. Twenty (11%) patients were diagnosed with pulmonary embolism (PE) before CDT was started, 18 (9%) patients had a retrievable IVC filter placed because of a free floating thrombus in IVC. No symptomatic PE occurred during treatment. Six patients had major bleeding. Coagulopathies were found in 85 patients (44.5%). During the observation period, three patients died from cancer and 11 patients had a recurrent DVT, of whom three had thrombosis of the stent and eight had DVT in a different segment. Furthermore, an in-stent restenosis (slightly more than 10−15%) was detected in five cases. These patients had no symptoms but were judged to be failures.

Overall median lysis time was 56 h (range 22−146 h). The median lysis time was 52 h (range 22−142 h) for the pulse-spray technique and 71 h (range 25−146 h) for the infusion technique ($p < .05$). A stent was placed in 106 limbs (52%). Self expandable stents (Wall Stent, Boston Scientific) were used in most cases ($n = 95$). In the remaining cases a Memotherm flex stent ($n = 6$), Smart stent ($n = 2$), Luminexx stent ($n = 1$), Sinus XL stent ($n = 1$), or Protegé stent ($n = 1$) were used. Patients with symptom duration >14 days ($n = 25$, 31 extremities) were more often men, aged <50 years, and more likely to have IVC atresia (12% vs. 32%), bilateral DVT (3.6% vs. 24%), and chronic post-thrombotic lesions (5% vs.23%). There was no difference in the duration of lysis or the frequency of coagulation defects. Symptom duration in this subgroup ranged from 15 to 24 days.

Chronic post-thrombotic lesions were detected in 15 patients (15 extremities). In nine patients the iliac vein could not be passed with the guide wire because of occlusion from groin level. In the remaining six patients the final venogram showed narrowing, irregular and thickened vein walls, collaterals, and decreased flow in the femoral vein. The cumulative rate of a patent and competent deep venous system at 7 years was 79% (Fig. 1).

First step univariate analysis showed that female gender, stenting, lysis duration <48 h, pulse-spray technique,

Table 1. Variables and results of testing of event (chi-square)/time to event (survival statistics).

Variable	Test	Better	% (No. legs positive[a])	Univariate chi-square p value	Univariate survival[b] p value	Multivariate survival[c] HR	95% CI	p value
Gender	Female	Female	72.3 (144)[d]	.025[e]	.004[e]	0.63	0.27−1.45	.28
Age	Above 50 years	<50 y	11.3 (23)[d]	.27	.23	2.14	0.80−5.77	.13
Side	Affected side = right	Left	71.9 (146)	.44	.33	1.14	0.46−2.80	.77
IVC atresia	Atresia present	No	15.3 (31)	.44	.21	1.29	0.48−3.51	.61
Stenting	Stent or no stent	Stent	52.2 (106)	.033[e]	.022[e]	0.71	0.28−1.76	.45
Duration of lysis	Above 48 h	<48 h	74.9 (152)	.033[e]	.053	1.28	0.42−3.87	.67
Type of lysis	Pulse-spray or not	Pulse	70.9 (144)	.008[e]	.12	0.15	0.05−0.48	.001[e]
Duration of symptoms	Above 2 weeks or not	<2 w	15.3 (31)	.005[e]	.0001[e]	2.78	1.14−6.73	.024[e]
Chronic post-thrombotic lesions	Lesions present or not	No	7.4 (15)	<.0001[e]	.0001[e]	19.3	7.29−51.2	<.0001[e]
Coagulation defect	Present or not	No	54.7 (111)	.91	.75	1.85	0.88−3.92	.11
Type of anticoagulation	LMWH or not (Heparin)	Heparin	34.5 (70)	.35	.46	2.47	0.82−7.45	.11

Event defined as first occlusion or detection of reflux by ultrasound.
HR = Hazard Ratio; IVC = Inferior Vena Cava; LMWH = Low Molecular Weight Heparin.
[a] How many of 203 legs were positive to test, e.g. first row, no. of female.
[b] Kaplan-Meier and log-rank test.
[c] Cox proportional hazard model, with Breslow correction for ties.
[d] Counts are number of patients.
[e] Significant p values (<.05).

symptom duration <14 days, and lack of chronic post-thrombotic changes were associated with better outcome (Table 1). Life-table intention to treat analysis showed that gender ($p = .004$), stenting ($p = .022$), duration of symptoms ($p = .0001$), and chronic post-thrombotic lesions ($p = .0001$) were significantly associated with outcome, whereas age, side, duration of lysis, IVC atresia, IVC thrombosis, and type of lysis (infusion vs. pulse-spray) did not affect outcome (Table 1). Finally, multivariate Cox regression analysis demonstrated that symptom duration >2 weeks (HR 2.78, 95% CI 1.14—6.73) and chronic post-thrombotic lesions (HR 19.3, CI 7.29—51.2) were the only factors significantly associated with poorer outcome, whereas the pulse-spray technique (HR 0.15, CI 0.05—0.48) resulted in better outcome (Table 1). Stenting was more often reported in patients with a longer history of symptoms but was not identified as an independent predictor in the multivariate analysis.

DISCUSSION

The therapeutic goal of this study was to accomplish complete thrombus removal by CDT. Three factors of the 11 tested by multivariate analysis were shown to be significantly associated with outcome. The clinical impact of the present findings is that symptom duration, type of infusion, and subclinical DVT episodes are important determinants of long-term patient outcome.

The present study demonstrates, for the first time, that outcome in terms of competent veins after CDT in ilio-femoral DVT is better in patients with symptom duration <14 days compared with patients with longer symptom duration. Symptom duration was assessed by asking the patients when they experienced their first symptom. Even though the study primarily included patients with symptom duration up to 14 days, 25 patients (31 extremities) with longer symptom duration were eventually included. The reason for extending the inclusion criteria was the promising initial results, which encouraged inclusion of selected patients with sub-acute DVT. These time limits are in accordance with the international classification, which recommends that having symptoms for less than 14 days is classified as acute DVT, whereas symptom duration between 14 and 28 days is categorised as subacute DVT, and more than 28 days as chronic DVT.[3] The subgroup of patients with longer symptom duration has poorer outcomes than other patients. This patient group has a priori a worse prognosis because of more cases of bilateral DVT, caval atresia, and chronic post-thrombotic lesions. A national multicentre registry with 221 patients with ilio-femoral DVT from the US used 10 days as the cutoff for differentiating between acute and chronic DVT.[4] There was complete lysis (grade III) in 34% compared with 19% in patients with a history of chronic DVT ($p < .01$). Conversely, grade I lysis (50% lysis) occurred more often in chronic cases than in acute cases (32% vs. 13%, $p < .01$). The CavenT study included patients within 21 days of onset of symptoms without stratifying according to symptom duration.[14] The recommendation from the American Venous Forum is to offer CDT for first time ilio-femoral DVT with a symptom duration less than 14 days.[15] The relevance of this statement is supported by the findings of the present study.

In the present study the infusion strategy was changed from continuous to pulse-spray. The hypothesis was that the jet like infusion delivered through the side holes of the catheter would exert a better “mechanical” effect on the thrombus as well as decreasing the lysis treatment time. Data on differences in outcome between pulse-spray and continuous infusion are sparse. The most recent studies and large scale trials have used the continuous infusion technique.[4,5,14,16] However, no comparative studies have

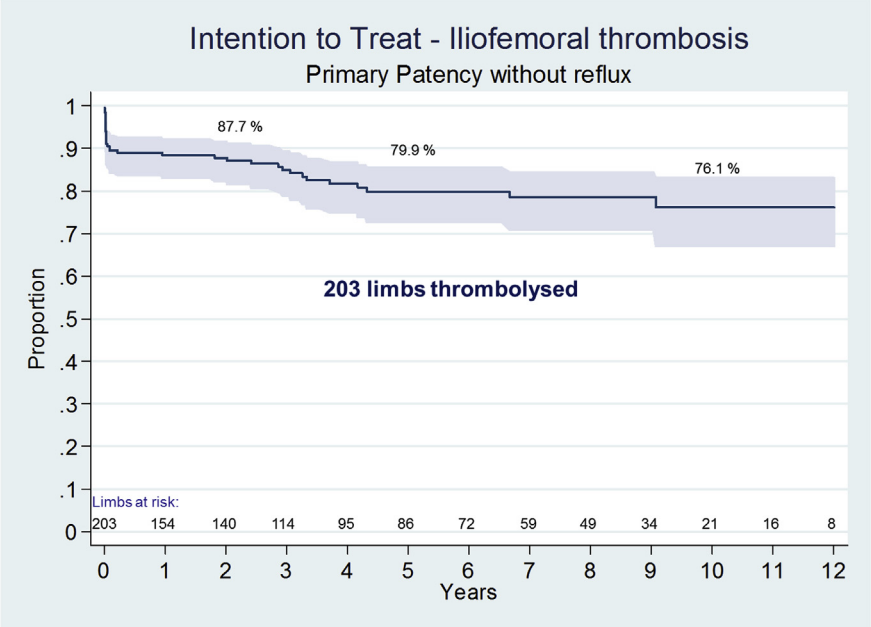

Figure 1. Cumulative rate of patent deep venous system without reflux (Kaplan-Meier).

examined the differences in outcome between the two infusion techniques in patients with DVT. A single randomised trial showed that pulse-spray was superior to continuous infusion for the treatment of intra-arterial thrombosis.[17] The finding in the Cox proportional hazard model seems to confirm this hypothesis.

It is not surprising that chronic post-thrombotic lesions visualised on the venogram during CDT will result in inferior results. It is well known that some DVT events are subclinical and therefore go unnoticed by the patient. Magnetic resonance venography may be used as a diagnostic tool before deciding whether a patient should be referred for CDT or not.[18]

In this study, 52% of the patients were stented. Stenting did not appear to be an independent factor for outcome in the multivariate analysis. This might be because of the limited number of patients. The stent rate of 52% in this study has not changed over the years, as 55% were stented in a previous study.[7] The literature reveals a considerable variation from 13% to 83%, with both extremes presented recently. Even though the rate of stent insertion was slightly lower than in other studies, the present outcomes are comparable or even better than previously reported.[4,14,16,19,20] Moreover, the high number (79%) of patients with patent deep veins without reflux at 7 years suggests that a sufficient number of stents were inserted. Unfractionated heparin and LMWH was equally effective as a concomitant anticoagulant during CDT (data not shown). LMWH is much easier to administer than unfractionated heparin.

It was demonstrated previously that vein patency is associated with less PTS and lower Villalta Scores.[11] This score may not be optimal for the evaluation of treatment success after CDT, as some patients with superficial incompetence may also develop PTS, and this score is not used routinely in the study institution. Moreover superficial incompetence can emerge without previous DVT. On the other hand patients with venous claudication cannot be assessed with the score.

Restoration of the venous outflow tract is fundamental for a successful result. Three recent publications support this notion. In a study from Comerota's group pre- and post-treatment venograms were used to quantify residual thrombus after CDT for ilio-femoral DVT.[21] Patients who had more than 50% residual thrombus in the treated vein segment had significantly higher CEAP grades and more severe PTS assessed by the Villalta score in 64 patients after 1.5 years mean follow-up. Similar findings were reported in the Norwegian CaVenT study. Lack of patency and reflux at 6 months were independent risk factors for development of PTS after 24 months.[22] A recent study reported 1, 2, and 3 year PTS rates of 8.8%, 19.6%, and 28.4% in patients treated for ilio-femoral DVT. Incomplete lysis (<50%, $p = .017$) was an important predictor of PTS.[23]

Strengths and limitations in the present study

The strengths of the present study are the meticulous retrieval of all relevant clinical information, the long-term follow-up, the large number of patients, and the assessment of competent and open deep veins using duplex ultrasound sonography.

This study also has some limitations. It is a non-randomised observational study including highly selected patients. Therefore, inferences on what is the optimal treatment of ilio-femoral DVT cannot be made from this study. Observational studies are prone to bias resulting from confounding by indication. As an example, younger patients, who may have better outcomes a priori, could be more likely to receive a stent or continuous lysis, if the clinician believes that this is the best treatment. This will introduce significant bias. It could be argued that self-reported symptom duration is an unreliable measure, as subtle symptoms may go unrecognised. However, when data collection began no objective means of determining thrombus age existed, so self-reports were the only available measure. Despite inclusion and exclusion criteria, case mix is inherent to observational research and may affect the generalisability of the present results.

CONCLUSION

In this observational study of CDT for ilio-femoral DVT, a multivariate Cox proportional hazard model demonstrated that symptom duration less than 2 weeks, absence of chronic post-thrombotic lesions, and use of pulse-spray technique for CDT resulted in better primary patency including normal valve function in the long-term than symptom duration more than 2 weeks, previous ipsilateral DVT, and the use of continuous infusion for CDT.

CONFLICT OF INTEREST

None.

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