Long-Term Results using Catheter-directed Thrombolysis in 103 Lower Limbs with Acute Iliofemoral Venous Thrombosis

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Iliofemoral venous thrombosis;
Catheter-directed thrombolysis;
Venous patency;
Venous reflux;
Chronic venous insufficiency;
Post-thrombotic syndrome

Abstract  Objectives: The long-term outcome of catheter-directed thrombolysis (CDT) in patients with acute iliofemoral venous thrombosis (IFVT) is evaluated in this study.
Material and methods: Patients presenting for treatment with IFVT between June 1999 and May 2007 were considered for treatment using CDT. The following inclusion criteria were used: first episode of IFVT, age below 60 years, age of thrombus <14 days and open distal popliteal vein. Ultrasonography (US) was used to verify the diagnosis. The popliteal vein was punctured under local anaesthesia using US guidance, and a multi-side-hole catheter with tip occlusion was placed in the thrombus. A solution of r-TPA was infused either continuously or using the pulse spray technique together with heparin. Any occlusion or residual stenosis in the iliac vein system was treated by stenting.
Compression stockings and anticoagulation treatment were given for at least 12 months. Patients with severe thrombophilias were treated for longer periods. The patients were assessed by colour-duplex US for assessment of patency and valve function after 6 weeks, 3, 6 and 12 months and afterwards on a yearly basis.
Results: A total of 101 patients with 103 extremities affected by iliofemoral venous thrombosis were included (median age; 29 years, 78 women, and 79 had left-sided thrombosis). A stent was inserted in 57 limbs. The median follow-up time was 50 months (range 3 days–108 months). At 6 years, 82% of the limbs had patent veins with competent valves and without any skin changes or venous claudication.
Conclusion: Treatment with CDT for IFVT achieves good patency and vein function after 6 years of follow-up in this highly selected group of patients. We suggest that results from...
Acute deep venous thrombosis, especially in the iliofemoral segment, is the cause of significant morbidity if left untreated. The thrombus may cause venous obstruction and/or valve insufficiency, which in time can lead to post-thrombotic syndrome with disabling venous claudication and skin damage and with severely impaired quality of life.

Endovenous treatments for venous thrombosis have been developed in the past 20 years. These aim to remove the thrombus in patients with acute deep venous thrombosis, especially in the iliofemoral segment. Catheter-directed thrombolysis (CDT) of iliofemoral venous thrombosis (IFVT) was the first of these new methods and was described in 1991 by Okrent et al., and 3 years later by Semba et al. The aim of the method is to restore the venous lumen and save the valves. Early restoration of normal veins tends to prevent chronic venous insufficiency and might minimise the risk for post-thrombotic symptoms, in the form of oedema, venous claudication, eczema or venous ulceration. These often disabling complications are seen in at least half of the patients with iliofemoral vein thrombosis, if treated by anticoagulation alone. The first review from 1999 showed promising early results, focussing mostly on the feasibility of the method, in terms of patency of the treated vein segments. This study presents the long-term results from Copenhagen with CDT for IFVT.

**Patients and Methods**

Patients included in this series are all consecutive patients with acute IFVT treated by CDT at the Gentofte Hospital from June 1999 to May 2007. The experience with the first 45 patients of this series in Copenhagen has previously been published. Data were collected prospectively, but supplemented with some retrospective clinical data. The patients were selected for treatment according to the inclusion and exclusion criteria listed in Table 1. Information about the treatment, its purpose and its possible adverse effects in the form of a small risk of pulmonary embolism, systemic and local bleeding was given to the patients initially, and informed consent was obtained. No patient refused treatment with CDT. All patients were managed by dedicated staff in the vascular department without the need for intensive care unit facilities.

The method of CDT and the follow-up programme used at the Gentofte Hospital has previously been described in detail. Table 2 contains an overview of the method, which has been practiced in our clinic. In patients where floating thrombus was seen in the infrarenal inferior vena cava, retrievable inferior vena cava filter (Günter Temporary Vena Cava Filter, Cook Medical), inserted from the contralateral common femoral vein, was used.

All patients were followed up in the outpatient clinic by clinical examination, supplemented by ultrasound examination of vein patency and valve function, as previously described. Patients were seen after 6 weeks, 3, 6 and 12 months and yearly thereafter.

**Follow-up**

All patients were followed up according to the protocol with exception of two patients, who moved out of Denmark and were lost to follow-up after 3 and 17 months, respectively. They both had patent veins with competent valves at the last known follow-up. The median follow-up time for the entire series was 50 months (range 3 days–108 months).

**Endpoints and statistics**

The ultimate endpoint was the development of post-thrombotic syndrome (PTS), especially venous claudication and skin changes. Since PTS can develop after several years with none or only mild symptoms, we chose to include the surrogate endpoint ‘patent vein without reflux’, the rationale being that in a patient with an open vein without reflux it is unlikely that PTS will develop. Survival analysis with Kaplan–Meier curves was used for this endpoint.

Secondary endpoints were the development of complications, especially re-thrombosis, pulmonary embolism (PE) and bleeding complications.

Statistical analysis was performed using STATA, version 10.0 (StataCorp, College Station, TX, USA).

**Results**

A total of 101 consecutive patients with acute IFVT affecting 103 lower extremities were included in the study. All patients were treated according to the protocol,

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**Table 1** Inclusion and exclusion criteria for catheter-directed thrombolysis of acute iliofemoral venous thrombosis (IFVT).

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode of IFVT</td>
<td>Previous ipsilateral DVT</td>
</tr>
<tr>
<td>Age &lt; 60 years</td>
<td>Major ipsilateral DVT</td>
</tr>
<tr>
<td>Age of thrombus &lt; 14 days</td>
<td>Birth in the last week</td>
</tr>
<tr>
<td>Open distal part of the popliteal vein</td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Cancer</td>
</tr>
<tr>
<td></td>
<td>Severe hypertension</td>
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<tr>
<td></td>
<td>Recent gastrointestinal bleeding</td>
</tr>
<tr>
<td></td>
<td>Recent cerebral hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Aplasia of IVC</td>
</tr>
</tbody>
</table>

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future studies should be presented as Kaplan–Meier plots using venous patency without reflux as the main outcome, since it is an early indicator of the clinical outcome. © 2009 European Society for Vascular Surgery. Published by Elsevier Ltd. All rights reserved.
although seven patients (eight legs) did not fulfil the inclusion and exclusion criteria.

The median age was 29 years (range 15–59 years), male/female ratio 23/78 and left/right ratio was 79/24. A self-expandable stent (Wall Stent, Boston Scientific) was placed on the left side in 55 cases and on the right side in two cases. Symptomatic PE was diagnosed with perfusion–ventilation lung scintigraphy before treatment in six patients.

A retrievable vena cava filter (Cook Medical) was inserted in seven patients and immediately removed after a successful thrombolytic procedure.

One male presenting with bilateral IFVT was diagnosed following treatment with testicular cancer and retroperitoneal metastases. The initial abdominal ultrasound examination did not reveal any abnormality, but a later computed tomography (CT) scan showed glandular tumour along the spine. Thrombophilia was seen in 54% of the patients, mainly factor V Leiden mutation, 35% used contraceptive pills and 22% were post partum. The median treatment time was 58 h.

Complications

No deaths occurred in this series following treatment. One patient was suspected of having a PE during treatment, but the ventilation–perfusion lung scintigraphy was normal. In two patients the procedure had to be terminated. One patient, due to sepsis without a known focus, was started on antibiotic treatment, and the thrombolytic treatment continued the next day. In another patient, development of an acute haematoma in the forearm necessitated fasciotomy. On the following day, phlebography of the iliofemoral segment was normal. A few weeks later, the patient recovered fully. This serious complication was a result of an arterial puncture in the radial artery a few days before thrombolysis. Two patients developed mild erythema and three patients had a small haematoma in the popliteal fossa, which did not need treatment. In several cases, slight bleeding along the catheter in the popliteal fossa was seen and managed with a simple compression bandage.

One patient complained of pain in the right groin in the sitting position some years after the treatment. A duplex scan showed that the open stent covered the proximal part of the common femoral vein. This was confirmed by the original venogram after placing the iliac vein stent 3½ years earlier. We suspected an association between pain and the position of the stent. The stent was removed and a 10-mm rPTFE graft was placed end to end as a new conduit. The pain disappeared later.

Failures with occlusion/stenosis

In one patient with bilateral iliofemoral thrombosis (the patient with cancer) bilateral CDT was unsuccessful. Four patients presented with chronic lesions; in three patients it was impossible to resolve the thrombosed femoral vein segment. These cases were considered to be chronic occlusions after earlier asymptomatic DVT, an assumption based on re-opened collaterals seen on the venogram. In the fourth patient, a long stenotic lesion with irregularity of the vein wall was the result after thrombolysis.

Three patients suffered re-occlusion of the iliac vein within 1 week of thrombolysis. For two of the patients, no further attempt was made to resolve the thrombus. One patient had re-thrombosis of her iliac stent 2 days after the initial thrombolysis, which was re-opened with CDT and an additional stent was placed in the external iliac vein.

Three patients suffered further episodes of DVT. In two of the patients, this was after 2 and 3 years, respectively, after cessation of anticoagulation treatment, involving the popliteal and crural veins, and was not suitable for re-thrombolysis. The last patient re-thrombosed about 1 year after the initial thrombolysis but was re-thrombolysed successfully. However, a re-thrombosis occurred again later, but re-thrombolysis was not attempted due to poor compliance to her anticoagulation treatment.

Failures with reflux

Deep reflux developed in six patients with patent veins during the follow-up period. Of these, one patient had reflux in both the femoral and the popliteal vein, one patient only in the femoral vein, and the rest only in the popliteal vein.

Open veins without reflux

Fig. 1 shows the results for all treated patients (intention to treat, ITT) with patent veins and normal valves after 6 years in 82% of the limbs. Fig. 2 shows an increased rate of
60% of the cases with PTS symptoms will occur huge costs to society. Based on the observation that at least disability and economic liability for the patient, as well as evaluated. These are the factors that lead to severe which vein patency and freedom from reflux have been clinical series of this treatment with long-term follow-up in

Discussion

The long-term results in this prospective single-centre clinical series of acute IFVT treated with CDT are still excellent in comparison with our first published series in 2005.7 Open veins without reflux were achieved in 82% of the affected lower extremities after 6 years without any mortality, or new PE and only a few cases of new DVT. The patients with restored venous iliofemoral segments showed no sign of PTS such as venous claudication, eczema or ulceration.

To our knowledge, this study describes the largest clinical series of this treatment with long-term follow-up in which vein patency and freedom from reflux have been evaluated. These are the factors that lead to severe disability and economic liability for the patient, as well as huge costs to society. Based on the observation that at least 60% of the cases with PTS symptoms will occur 2–3 years after the thrombotic event, the long follow-up interval in this series gives evidence of a lasting effect.8

Mortality of 0.4% has been reported in The National Venous Registry in 1999.9 PE has been reported in a few papers in 1–13% of the treated cases.9–12 Major bleeding is reported in up to 10% in some studies, but many papers have reported only minor bleeding complications.

There is no consensus as to whether or not an IVC filter is necessary. The figures for PE complications listed above concern patients mostly free of thrombus involvement of IVC. It has been shown that 22% of pelvic vein thromboses propagate into the IVC without a higher risk for PE compared with DVT in femoral or iliac vein segment alone.13 In another paper, visible emboli in a retrievable filter were found in almost half of the cases and most in patients with a hypercoagulable state, not necessarily causing symptomatic PE.14 However, a filter without emboli may be the result of thrombus lysis within the filter by the treatment given in the limb. Filter insertion itself may also be troublesome. We decided to place a filter if thrombus was found to be floating, in which case it was inserted from the contralateral groin with great caution. This strategy seems wise until further evidence is obtained. A situation with a patient with poor pulmonary reserve due to earlier PE could be an indication for filter placement.15

Our series included seven patients (eight legs) with aplasia of the inferior vena cava. In the first case the venogram revealed the diagnosis, which was in contrast to what was suspected on ultrasound imaging, and led to intervention with thrombolytic therapy. After the initial successful treatment of the first patient, it was decided to offer treatment to these patients outside the protocol, and a total of seven patients (eight legs) were included in this study. All these patients had patent veins without reflux at follow-up. Very few papers have published results on this treatment option.11,16

In our opinion, the use of intermittent pneumatic compression (IPC) to these patients has been beneficial. It has been shown in a small comparative study that the use of IPC of the foot and calf during bed rest can reduce oedema without increasing the risk of PE. IPC resulted in better initial complete lysis, late patency and better valve function compared with that in the control group.17

In contrast to many other publications concerning IFVT, this series excluded patients with thrombus affecting the popliteal and calf veins. If these patients were included, it would have had a negative impact on the results. The untreated crural veins would not have been thrombolysed.9 Attempts to puncture and thrombolysie an occluded popliteal vein in cases of distal DVT is of no benefit to the patient because one of the basic principles with CDT is to have ongoing upstream blood flow to maintain the cleared vein segments open during the procedure.18

Streptokinase has been abandoned due to the allergic complications, and now urokinase, recombinant tissue plasminogen activator or reteplase are used in the published trials. One paper demonstrated no difference in the results concerning safety or efficacy of these drugs.19

There are other conflicting areas comparing results after CDT. Many series have included patients with cancer, previous ipsilateral DVT and duration of symptoms prior to treatment up to 4 weeks. This co-morbidity and symptoms

Figure 2

86% for the fraction of patients who fully complied with the protocol (Table 3).

Post-thrombotic symptoms

All patients with patent veins and normal valve function showed no sign of dermal pigmentation, ulceration or venous claudication at follow-up. In this group, seven patients had slight oedema, according to the CEAP clinical class C-3; of these, five had superficial reflux (four great saphenous vein and one small saphenous vein). Three other patients had a slight feeling of heaviness in their affected limb.

Table 3 The series of 101 patients with 103 limbs.

<table>
<thead>
<tr>
<th>Limbs treated per protocol</th>
<th>89</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention to treat with CDT</td>
<td>103</td>
</tr>
<tr>
<td>In the patient with cancer</td>
<td>2</td>
</tr>
<tr>
<td>With chronic changes: SFV, CFV, SFV + CFV, stenotic SFV</td>
<td>4</td>
</tr>
<tr>
<td>With caval atresia</td>
<td>8</td>
</tr>
</tbody>
</table>

Patency without reflux

[Image of Kaplan-Meier Plot]
of long duration may negatively affect the outcome, and emphasise the importance of including a detailed description of the patients included in any published series. An acute DVT should be defined as symptoms present for 14 days or less and/or imaging indicating the venous thrombosis having occurred within 14 days.\textsuperscript{15}

Many series describe the outcome divided into vein segments with complete or partial clot resolution. At 1 year, the outcome might be twice as good, in terms of patent veins, after initial total clot removal compared with partial clot removal.\textsuperscript{9} The effort should be directed at removing all of the thrombus, which was achieved in all our patients with primary DVT. Our methods included replacing the catheter in the remaining thrombus when necessary and then to continue thrombolysis for additional 6 h after total clot removal in cases of sustained elevation of D-dimer and to insert a stent, even in cases with minor iliac stenosis.

One major bleeding complication occurred. The case emphasises that a medical history, together with a very careful objective investigation of the patient, is mandatory before administering a thrombolytic agent. Another aspect of these considerations to avoid bleeding episodes is the use of a secure technique with US guidance for puncturing the popliteal vein.

There are very few publications with long follow-up comparable to our study. Work from 2001 compared a group of 33 patients treated with anticoagulation alone with a group of 18 patients treated with CDT. The outcome presented in a Kaplan—Meier plot showed 3 times better patency of 69\% after 5 years for the group treated with CDT. Reflux was not mentioned as an endpoint. Long-term symptom resolution was 78\% in the CDT group compared with 30\% in the group treated with anticoagulation.\textsuperscript{20} A more recent publication reporting the outcome in 34 patients showed poor results with occlusion in almost 60\% of the stents after 3 years. A stent longer than 6 cm was found to be the cause of failure, but there were severe methodological problems.\textsuperscript{19} Reflux was found in 32\% after 24 months in another study with 28 patients.\textsuperscript{11}

In a study with almost comparable groups, the patients treated with CDT experienced better quality of life (QOL) compared with patients treated with anticoagulation alone after median 22 months of follow-up.\textsuperscript{21}

A randomised controlled trial (RCT) published in 2002 compared CDT in a group of 18 patients with a group of 17 patients treated with anticoagulation. After a short follow-up time of 6 months, the CDT group had a patency rate of 72\% compared with 12\% in the group treated with anticoagulation. The outcome of venous reflux assessments mirrored those of patency, which were 12\% compared with 41\% in favour of CDT.\textsuperscript{22}

Another recently published and still ongoing RCT from Norway (the CaVenT study) with 50 patients treated with CDT and 53 patients in the control group receiving standard treatment alone did not demonstrate the same convincing results as the RCT from 2002. At 6 months, patency of the iliofemoral segment was 64\% in the CDT group and 36\% in the control group corresponding to an absolute risk reduction of 28\%. Femoral venous incompetence was found in 60\% and 66\% among the CDT-treated patients and controls, respectively. No significant correlation was found between the lysis grade or use of additional angioplasty/stent and 6 months’ patency.\textsuperscript{23}

**Conclusion**

Patient veins without reflux were achieved in 82\% of patients affected by iliofemoral venous thrombosis treated with CDT after a median of 50 months of follow-up. For patients strictly following the protocol, the result was 86\%. This clinical series of 101 patients had very strict inclusion criteria for inclusion, which proved to be very efficient in reducing the post-thrombotic complex of symptoms, compared with traditional anticoagulation alone. We strongly recommend that future reports present results using survival statistics, as a Kaplan—Meier plot of competent veins, defined as open veins without reflux. Future RCTs will show if anticoagulation alone still has a role for this selected group of patients.

**Conflict of Interest/Funding**

None.

**References**


