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Catheter Directed Thrombolysis for Treatment of Ilio-femoral Deep Venous Thrombosis is Durable, Preserves Venous Valve Function and May Prevent Chronic Venous Insufficiency

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Objectives. *To investigate the results of catheter directed thrombolysis offered to patients with acute femoro-iliac deep venous thrombosis (DVT).*
Design. *Retrospective analysis of all patients treated with this modality at Gentofte Hospital until December 2003.*
Material. *Forty-five consecutive patients treated between June 1999 and December 2003 with a median age of 31 years. All patients had femoro-iliac DVT with an average anamnesis of 6 days.*
Methods. *All patients were treated by catheter directed infusion of alteplase into the popliteal vein. After thrombolysis residual venous stenoses were treated by percutaneous balloon angioplasty (PTA) and stenting. Patients were followed with color-duplex scanning for assessment of venous patency and reflux.*
Results. *Forty-two of 45 (93%) of cases were treated successfully with reopening of the thrombosed vein segments. In 30 of 45 cases a residual stenosis was treated by PTA and stenting. Only one serious complication was observed: Compartment syndrome of the forearm where arterial punctures had been taken. After an average of 24 months follow-up were no cases of re-thrombosis among the 42 patients discharged with open veins. Only two of 41 with presumed normal venous valve function prior to DVT developed reflux during follow-up.*
Conclusion. *In this selected patient group, catheter directed thrombolysis seems effective in treating acute DVT, it appears durable and preserves venous valve function in the majority. The method needs to be tested in a randomised controlled trial.*

Keywords: Deep venous thrombosis; Thrombolysis; Venous reflux; Deep venous insufficiency.

Introduction

Deep venous thrombosis (DVT) remains the primary pathogenetic mechanism for development of chronic deep venous insufficiency (CDVI), which may result in chronic pain, oedema and ultimately venous ulceration of the lower limb. Also, DVT may in the acute phase give rise to pulmonary embolism, which in worst case may be fatal. Treatment in the acute phase is directed towards prevention of further thrombosis and pulmonary embolism and significant risk reduction may be obtained by anticoagulation with heparins and warfarin. On long term, anticoagulation may be continued if the patient has increased risk of recurrence of DVT, i.e. because of hemostatic disorders. However, CDVI develops in many patients after DVT and with serious symptoms affecting quality of life in 33–87%.[1–6]

The pathogenetic mechanism for development of CDVI may be either that of venous reflux due to destruction and/or insufficiency of the venous valves or due to chronic venous obstruction. In either case, venous hypertension develops and results in the above mentioned symptoms. Because venous thrombi in the majority of cases are partly or totally autolysed within a few months, venous reflux is by far the most common of the two mechanisms, since, the venous valves most often are destructed during the recanalisation process.[7]

Venous thrombectomy and systemic thrombolysis was performed experimentally for many years, however, their true value was never convincingly proven in randomised controlled trials. In the only published randomised trial, Plate *et al*. showed that, although the operated group (venous thrombectomy)

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had better outcome than the group treated with anticoagulation, none of the two groups did very well in the long run.[8] In recent years, a number of reports has indicated that local thrombolysis, directed through an intravenous catheter into the venous clot, resulted in successful lysis of the thrombus and high percentage of the reopened veins appeared patent within the first year.[9–13] Lately also venous reflux appears to be avoided in the majority of patients treated with local thrombolysis.[13–15] Only one small, randomised trial with 6 months follow-up has been published indicating that DVT treated with thrombolysis results in superior patency and better preservation of valve function.[15]

The main goal of treatment of DVT should be to prevent CDVI on long term, thus, not only patency of the thrombolysed vein segments is of relevance, venous valve function may be at least as important. In 2002, we published our initial experience with our first 12 patients treated with local catheter-directed venous thrombolysis.[13] We had an initial success rate of 83% and found all lysed veins being patent with normal venous valve function at 5 months follow-up (median). The present study reports our experience during the first 4.5 years where we have offered local thrombolysis in selected cases with femoro-iliac venous thrombosis.

Material and Methods

The first of the 45 consecutive patients in this study was treated 16th of June 1999 and the last December 3rd 2003. Seven were males and 38 females, with a median age of 31 years (range 15–57 years). All patients had femoro-iliac DVT and had accepted treatment with catheter-directed thrombolysis, a treatment that had been described for them as being on experimental basis.

All patients were referred with diagnosed deep venous thrombosis mainly from departments of internal medicine, in hospitals from all over the country. Only patients with a short anamnesis (< approximately 14 days) without obvious contraindications for thrombolysis were seen. On admission, all patients were seen by a consultant in vascular surgery and a specialist in haemostasis in order to assess the clinical history and status of the patient.

Inclusion criteria for thrombolysis were DVT involving the ilio-femoral segment and an anamnesis <2 weeks. Also, one deep vein was required to be open in the popliteal fossa since, our technique relied on the catheter being introduced through the popliteal vein.

Exclusion criteria included the following: Age >60 years, malignancy or other concomitant chronic or potential life-threatening disease, bleeding disorders, uncontrolled hypertension and recent surgery. Also, patients with a history of previous ipsilateral DVT or CDVI were excluded.

Investigations prior to thrombolysis

On admission patients were examined by color-Doppler ultrasound for assessment of the venous system. Patients fulfilling the inclusion criteria were informed about the treatment options including that local thrombolysis was an offer and that this treatment remains experimental without proven long-term results. Patients were informed about a small risk of pulmonary embolism and systemic bleeding in addition to the possibility of local complications in the region of puncture (poples). Prior to thrombolysis all patients were given low molecular weight heparin (tinzaparin) 100 IE per kg twice daily and oral anticoagulant therapy initiated at the referring hospital was discontinued. The heparin dosage was adjusted according to anti-Xa levels.

Patients accepting thrombolysis were screened for thrombosis promoting factors by evaluation of factor V Leiden mutation, protrombin mutation 20210, protein C, protein S, antithrombin, plasminogen, anticardiolipin antibodies, lupus anticoagulans and homocystein. In addition, INR, platelets, fibrinogen, D-Dimer, activated partial thromboplastin time (APTT), hemoglobin, creatinine, sodium and potassium was assessed.

All patients with pulmonary symptoms had pulmonary scintigrams performed prior to and after thrombolytic therapy.

The diagnosis of DVT was confirmed by a venogram performed by direct puncture of the popliteal vein (see below). In this manner the precise extension of the DVT could be estimated. The contralateral iliac venous system was examined either by ultrasonography or by venography to secure the run-off on this side and the presence of an open vena cava (one case with partial aplasia of the vena cava was eventually treated, see below). In doubt of the presence of a normal vena cava a CT scan was performed. If a CT scan was not performed an abdominal ultrasound examination was done to exclude major tumours or other masses that could compress the venous system.

In the angiosuite, the popliteal vein was punctured using ultrasound guidance allowing for introduction of a lysis catheter. In the beginning we used a double catheter—coaxial catheter system (Mewissen Infusion

Catheter/Katzen Infusion Wire; Boston Scientific) with the intention to infuse the thrombolytic fluid into most of the thrombus. A starting dose of 1 mg alteplase (rt-PA) + 1000–5000 i.e. unfractionated heparin was used followed by continuous infusion of 1 mg rt-PA + 1000 i.e. heparin per hour. Later (from patient number 10) a long lysis catheter with a tip occluder and side holes over 40–50 cm was used (Pro Infusion Catheter; AngioDynamics), covering most of the extension of the thrombosis. Treatment started with 'pulse-spray' technique, where 10 mg rt-PA + 1000–5000 i.e. heparin was injected over the first 15–30 min in the attempt to shorten the overall treatment period. Hereafter, thrombolysis continued as described with the first nine cases, however, with the rt-PA dissolved in a larger volume of fluid (100 ml/h). Initially, pulse spray was performed manually for approximately 15 min by the radiologist; during the last year of the present series an automatic system was used in the ward additionally, which continuously generated a pulse every 15 s.

Control venograms were performed every day and when all clot had been lysed, and a stenosis maybe uncovered, this was dilated and stented before catheters were removed. In cases were all visible thrombus had been lysed, but the D-Dimer remained above 10 mg/l lysis was continued for 6–24 h.

During the period of i.v. infusion of rt-PA, the patient remained in bed with a continuous compression device on the calf (sequential compression device: SCD pump).

Blood tests prior to treatment are mentioned above. When rt-PA infusion was initiated, treatment was monitored with APTT, thrombin time, fibrinogen, antithrombin, fibrin D-Dimer, hemoglobin and platelets. Depending on prior anticoagulant treatment INR or anti-Xa was measured for adjustment of heparin starting dosage. During treatment, heparin dosage was adjusted to APTT between 80 and 100 s. After lysis was terminated patients were started on warfarin and was also treated with low molecular heparin (tinzaparin) 100 IE per kg twice daily for 14 days.

Measurement for long graduated compression stockings was taken using the healthy leg during thrombolysis so the patient could be discharged with a relevant compression.

Patients were followed up at regular intervals: After 6 weeks, 3, 6 and 12 months. Thereafter patients were invited on a yearly basis. At follow-up patients were seen by a consultant in vascular surgery, and a color-Doppler investigation was performed to assess venous patency in the horizontal position and valve function (reflux) in the standing position. Reflux was assessed in the femoral and popliteal veins and defined as retrograde flow following release of compression of the calf muscles lasting more than 0.5 s.

At 1 year all patients were invited to a venogram.

All patients were treated with warfarin for at least 12 months. Only patients with high risk of re-thrombosis (i.e. serious coagulant defects such as antithrombin deficiency, homozygous factor V Leiden mutation, protein C and S deficiencies etc.) remained on warfarin.

Results

Forty-three of the 45 patients had thrombosis involving the iliac veins. The two without iliac involvement had thrombosis of the superficial femoral vein and one also of the proximal popliteal vein. Five patients had DVT confined only to the iliac veins (Table 1). There were seven cases of right sided DVT and 38 left sided. Despite our attempt to exclude patients with previous DVT on the affected limb, three patients were included: Two patients who revealed findings, which during treatment were judged to be due to previous DVT (one with remote symptoms not identified pre-treatment, and one without any symptoms at all). One patient had a history of ipsilateral femoral DVT 6 years before the present episode—diagnosis confirmed by venography. This patient had pathological fast venous filling time, as assessed by venous pletysmography, performed 5 years before the DVT qualifying for thrombolysis. Also, one patient with partial aplasia of the vena cava was treated since, her left leg was severely affected by the thrombosis.

The duration of symptoms was in median 6 days (1–14 days) and was used as the estimate of when the thrombus had developed. In many cases the initial symptom was pain in the groin, iliac fossa or lower back appearing days before the actual swelling of the limb. When assessing the time of symptoms we used the first symptom, i.e. pain before swelling of the limb. In nine cases the lower limb DVT was associated with symptomatic pulmonary embolism.

There were no cases in which planned thrombolysis was not conducted as planned. In only one case the

Table 1. Extension of thrombus prior to thrombolysis

Venous segments with thrombus	
I	5
I+F	34
I+F+P	4
F	1
F+P	1

I, iliac vein; F, femoral vein; P, popliteal vein.

treatment was stopped early due to a complication (compartment syndrome of the forearm—see below), however, the thrombosis was lysed at that time and the remaining stenosis was stented the following day.

The median time of treatment (infusion of rt-PA including endovascular management) was 71 h (range 25–146 h). When lysis was completed, 30 of the 45 occluded veins (67%) revealed underlying stenoses in the iliac veins. Two of the stenotic lesions were among the seven (28%) patients with right sided DVT whereas the remaining 28 were found among the 38 (74%) with DVT on the left side. All were treated with balloon angioplasty and stent (mainly Wall Stent, Boston Scientific, but also Memotherm, Bard, and Smart Stent, Cordis).

Technical success with re-opening of the deep veins was obtained in 42 of 45 (93%) cases (Table 2). Partial lysis and re-opening was obtained in two of the last three cases: One case turned out to have chronic superficial femoral vein (SFV) occlusion, which was evident as the catheter barely could be passed through the occlusion. By re-questioning the patient he did actually have symptoms of previous DVT of that leg. In addition to the chronically occluded SFV the patient also had iliac vein thrombosis, which was successfully dissolved. At follow-up, the SFV has remained occluded but the lysed iliac vein has remained patent at 49 months follow-up. The second patient probably had a chronic occlusion of the common iliac vein since, thrombolysis of the femoral and external iliac vein was successful and the patient became asymptomatic also without reflux at follow-up. The last patient underwent 120 h of rt-PA infusion and the deep veins were partially re-opened, however, with some residual thrombus remaining. This patient re-thrombosed before discharge and no further attempts were done.

Complications were observed in seven cases (16%), however, only severe in one case. A 23-year-old woman with pulmonary embolism secondary to her DVT had arterial punctures taken in her left arm prior to lytic therapy. After 16 h of thrombolysis she developed compartment syndrome of her right forearm, most probably due to the previous punctures of the radial artery. Fasciotomy was performed and later closed and the patient has no sequelae at 4 months follow-up. Additional four patients had minor bleeding complications, however, in none so that it prevented continued lysis. The bleeding was mainly confined to the puncture site in the popliteal fossa and in one case 6 days post partum some vaginal bleeding occurred (not requiring transfusion). One patient had a skin rash (erytema), however, the patient was simultaneously treated with penicillin due to high temperature. One patient re-thrombosed 2 days after termination of 146 h lysis. This patient underwent re-thrombolysis for 46 h before discharge and the deep veins have remained open with normally functioning valves at 24 months follow-up.

Table 2. Results of thrombolytic therapy after a median of 24 months follow-up

Number of pts. Treated	45
Technical success (thrombus lysed)	42 (93%)
Number of patients discharged with open deep veins	42 (93%)
Number of re-occlusions after discharge	0
Number of patients without venous reflux	39 (96%)*

* One patient had pathologically fast venous refilling time demonstrated 5 years before thrombolysis and thus, most probable venous reflux already.

Hemostatic predisposing factors was identified in 30 of the 45 patients (67%), of whom 15 had two factors (factor V Leiden heterozygote, lupus anticoagulans, anticardiolipin antibodies, protein S deficiency, hyperhomocysteinemia and prothrombin mutation).

Median follow-up time was 24 months (range 1–51 months). All of the deep veins that were opened in the 42 patients, who were discharged after successful thrombolysis, remained patent at follow-up. The two patients who could not be recanalysed remained with chronic occlusions of their SVF and common iliac veins, respectively. The patient with chronic common iliac occlusion, who had her femoral and external iliac veins re-opened by thrombolysis was asymptomatic without reflux at 24 moths follow-up. The patient with chronic SFV occlusion had tendency to oedema of the ipsilateral lower limb and reflux had developed in the popliteal vein (seen last 49 months after treatment). In the 42 patients who had successful thrombolysis, reflux was found in three patients. However, one of these was the patient with previous DVT and short venous filling time, as mentioned previously. In the two others, with presumeably normal functioning valves prior to DVT and thrombolysis, reflux was discovered at 24 and 49 months follow-up. Thus, in 39 of 41 (96%) patients where venous valve function presumably was normal before DVT, it remained normal at follow-up. Interestingly, none of the three patients with reflux presented any symptoms at follow-up (40, 49 and 49 months).

The patient included with atresia of the vena cava had the SFV and iliac veins opened and venous drainage was through large lumbar veins. This patient was asymptomatic without reflux 8 months after treatment.

Discussion

The presented results compare favourable with those reported in the literature. Previous studies have reported a primary success rate of 80–90% concerning total or partial recanalisation of the thrombosed deep veins. In a report from a national register Mewissen *et al.*[12] found a primary success rate of 83% although only 31% had total lysis of all thrombosed segments and 52% partial thrombolysis. Bjarnason *et al.* treated 77 patients with ilio-femoral DVT and without malignant disease and obtained total or partial thrombolysis in 89%. We reopened the thrombosed deep veins in 93% of cases; however, our patient material was highly selected, probably accounting for our high primary success rate. In our three failures, chronic occlusion of some of the occluded venous segments may have contributed to the lack of success in at least two of the cases. It is well known that venous occlusion may occur without symptoms, thus, our patients may have been unaware of previous venous occlusive disease.

The patency rate was very good; all patients discharged with open veins (93%) also had open veins after the average of 2 years follow-up. Bjarnason *et al.*[11] reported a 2-year patency of 78% and Ly *et al.*[14] found that all of those who initially had complete lysis remained patent at 20 months whereas those with only partial lysis had a lower patency rate. That our patency rate seems superior to that reported by others is probably due to a combination of our strict selection criteria and that we chose to treat all remaining stenoses by balloon angioplasty and stent. Ly *et al.*,[14] who treated a comparable patient material, only used endovascular treatment following lysis when a pressure gradient >3 mmHg was associated with the remaining stenosis. Thus, only four of 28 (14%) patients were treated endovascularly in this material as compared to our 65% who were dilated and subsequently stented.

Three studies have evaluated venous valve function after thrombolysis. Elshawary and Elzayat found significantly fewer (only two of 18 (11%)) to have developed reflux 6 months after treatment with thrombolysis as compared to seven (41%) in the group treated with anticoagulation.[15] Ly *et al.* reported that nine of 28 (33%) developed reflux at 2 years follow-up apparently related negatively to the degree of lysis (less reflux the better degree of lysis).[14] Laiho *et al.*[16] found 44% of treated patients to have preserved venous valve function 2–3 years after treatment. We experienced even better results since, only two of the 42 (4%) discharged with patent veins developed reflux (one patient with reflux at follow-up most certainly already had this at the time of thrombolytic therapy). An explanation for this high degree of valve preservation could be that our median time between first symptoms and lytic therapy was only 7 days.

The fact that venous function remained preserved after 2 years may indicate that the risk of developing post thrombotic syndrome in long term may not be so high for these patients. Serial ultrasound studies on patients with newly developed DVT has shown that reflux indeed develops within few months after the acute thrombosis,[7] a finding which could support a good prognosis for patients undergoing successful lysis with preserved venous valve function. Looking at the patients who did develop reflux, one was among the two who probably had a history of DVT, which could account or contribute to the damage of the venous valves.

Despite attempts to exclude patients with previous DVT and vena cava atresia three patients were included: Two with previous ipsilateral DVT and one with vena cava atresia. In both cases with previous DVT previous relevant symptoms were not clarified on admission and in one case remote symptoms had been present. The patient with vena cava atresia was an 18-year-old girl with severe symptoms from the affected limb where the femoral and iliac veins were occluded. The thrombosed segments were successfully re-opened and she became asymptomatic with normally functioning veins. The success in this case probably reflects that treatment resulted in restoration of her usual venous run-off.

Systemic thrombolysis has been performed in the past but was never convincingly shown to be of major benefit, although some improvement was reported in single centre series. No randomised trial has been published that has demonstrated a clear advantage compared to conservative treatment with anticoagulation alone. In a meta-analysis Comeraota *et al.* showed that systemic thrombolysis resulted in significant or complete lysis in 45% compared to only 4% of those treated with anticoagulation. Thus, less patients will develop CDVI after systemic thrombolysis as compared to anticoagulation which, however, has been reported in only to controlled trials, summarised by Comerato.[17] In a recent report, Laiho *et al.* followed 16 patients who had prior systemic thrombolysis and 16 patients who was treated with catheter directed thrombolysis. Two to 3 years after the acute avent, patients treated with catheter directed thrombysis fared better both with respect to preserved venous valve function and clinical symptoms.[16] This was, however, not a randomised trial.

In the only published randomised study venous thrombectomy was shown to improve the long term outcome in the operated group, however, still the

majority of the treated patients (60%) went on to develop chronic venous insufficiency.[8] Considering that we found 65% to have an underlying stenosis after lysis of the thrombus, one reason for the limited success of venous thrombectomy could be that these stenoses were left untreated and potentially caused re-thrombosis at a later stage. The good results presented in this study and by others do, however, not make it tempting to undertake a comparative study between catheter directed lysis and venous thrombectomy. Even if the latter could result in the same rate of technical success and long term patency and preserved venous function, it would seem unrealistic to have as low a perioperative morbidity.

Another reason to favour catheter based thrombolysis is the theoretical less damage to the venous endothelium. In a study where thrombosis was induced in the iliac vein in dogs, Cho *et al.* investigated the effect of no treatment, venous thrombectomy and catheter based thrombolysis.[18] The experiment showed that thrombolysis was the method, which with least damage to the vessel wall and valve function and least thrombogenicity resulted in recanalisation of the vein.

There may be a number of reasons for the good results obtained in our study. First of all, our patients were highly selected. This policy was chosen since, we were introducing a new and experimental treatment algorithm to replace a safe and proven treatment: Anticoagulation. Although it is well known that anticoagulation alone does not prevent CVDI, it is effective in preventing pulmonary embolism and death. Thus, we wished to introduce catheter-based thrombolysis with the highest possibility of success. Finally, treatment of acute DVT is offered as a combined effort by three departments: Department of vascular surgery, department of radiology and the thrombosis centre.

The findings of this study support those previously published and clearly indicate that catheter based thrombolysis may be a superior treatment compared to anticoagulation alone. The present study adds to the literature showing that not only may the opened veins remain patent, the valve function remain preserved making it tempting to believe that treated patients may remain asymptomatic on long term. A study by Comerato *et al.* even indicate that quality of life is better after catheter directed thrombolysis when compared to anticoagulation.[19] However, despite these promising results on short as well as long term, randomised trials needs to be designed and conducted. At present only one small trial has reported early results indicating that catheter directed thrombolysis results in better outcome as compared to anticoagulation. Thirty-five patients were randomised and both patency and venous valve function was significantly better at 6 months follow up.[15]

In conclusion, although the literature quite clearly indicates that catheter-based thrombolysis is superior to anticoagulation in selected patients, other studies will be needed to support the present data and to identify the patients who will benefit from thrombolysis.

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