European Journal of Radiology 81 (2012) 1197–1202

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Catheter-directed thrombolysis of proximal lower extremity deep vein thrombosis: A prospective trial with venographic and clinical follow-up

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ARTICLE INFO

Article history:
Received 26 January 2011
Received in revised form 17 March 2011
Accepted 23 March 2011

Keywords:
Vein thrombosis
Thrombolytic therapy
Post-thrombotic syndrome
Deep vein thrombosis
Catheter-directed thrombolysis

ABSTRACT

Purpose: To prospectively evaluate the primary and long-term venographic and clinical results of catheter-directed thrombolysis in the treatment of proximal deep vein thrombosis (DVT) of lower extremity.
Materials and methods: Fifty-six patients with mean age of 48 (range 15–81) years with acute DVT (symptom duration of less than 2 weeks), extending to high femoral (16 patients) or iliac vein (40 patients) were treated with selective catheter-directed thrombolysis. The mean total dose of 3.8 (range 1.0–8.1) million units of urokinase was administered during a mean of 39 (range 6–72) hours. Endovascular stenting was performed in 9 of the iliac DVT patients.
Results: Complete procedural venographic success was achieved in 79% of patients. Major complications were noted in 7% of patients and the total rate of complications was 13%. Mean venographic follow-up was 3.5 years (range 3 months to 9.6 years); well preserved femoral vein valves and fully recanalized deep crural veins were observed in 83% and 57% of patients. Normal clinical findings in the affected limb were noted during the latest follow-up visit in 67% of patients. Clinical post-thrombotic syndrome occurred in 9% of patients.
Conclusion: Catheter-directed thrombolysis achieves good primary success with acceptable complication rate and effectively reduces prevalence of post-thrombotic syndrome.

1. Introduction

The immediate goals of the successful management of deep vein thrombosis (DVT) include the relief of acute symptoms and the prevention of clot propagation and subsequent pulmonary embolism. Though less appreciated in the initial treatment of acute DVT, post-thrombotic syndrome (PTS) often causes severe late morbidity. The pathophysiology of this syndrome is ambulatory venous hypertension with valvular incompetence and luminal obstruction [1]; there are convincing data on a strong association between venous valve destruction and reflux with the development of PTS [2]. Thus, the aim of acute DVT therapy is restoring patency and maintaining valvular function by eliminating thrombi in the deep venous system.

The traditional therapy for iliofemoral DVT is unfractioned or low-molecular-weight heparin followed by warfarin. However, only approximately 5% of patients treated with anticoagulants have significant or complete lysis, and the vast majority (up to 70%) exhibit no objective venographic clearing or have thrombus extension [3,4]. Rapidly restored deep vein patency is important. Follow-up studies have revealed that as many as 95% of patients with proximal (vena cava, iliac, and/or femoral vein) thrombosis treated with only anticoagulant therapy have severely compromised muscle pump function and valvular competency, 30–75% have symptoms of PTS, and 10–40% suffer from severe limb edema, chronic pain, and/or ulcers [4,5]. Systemic thrombolytic therapy, which was adopted in the 1970s, is up to 3.7 times better than heparin for acute thrombus resolution [6]. Less than half the patients treated with systemic thrombolytic therapy have good to excellent venographic outcomes, up to 40% fail to improve or worsen, and there seems to be no decrease in pulmonary embolism and death [6,7]. However, there might be some decrease in the incidence of PTS compared to heparin [7].

Because of the lack of effectiveness of anticoagulants and systemic thrombolytic therapy, expectations rose in the 1990s with local, catheter-directed therapy for DVT due to the efficacy of selective thrombolysis and associated endovascular therapy in peripheral arteries that resulted in more rapid thrombus dissolution and reduced hemorrhagic complications compared to systemic infusion. Although these therapies have been used in selected cases

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doi:10.1016/j.ejrad.2011.03.068

Table 1
Baseline characteristics of the patients ($n = 56$).

Age (years)*	54 (15–82)
Gender (male)	26 (46%)
BMI $\geq$ 30 kg/m^2	16 (29%)
Diabetes	4 (7%)
Oral contraceptive use	12 (21%)
Current smokers	11 (20%)
Recent surgery (<3 weeks)	5 (9%)
Malignancy	3 (5%)
Recent fracture (<3 weeks)	1 (2%)
Previous deep venous thromboembolism	6 (11%)
Venous anomaly	4 (7%)
Factor V Leiden	12 (21%)
Prothrombin gene mutation	2 (4%)
Lupus anticoagulant	2 (4%)
Protein S deficiency	1 (2%)
Myeloproliferative disorder	2 (4%)

of proximal DVT for more than 20 years, the data on their primary success and especially the long-term results are still based on a limited number of patients; most importantly, their effectiveness in PTS prevention is not well known.

The purpose of this prospective study was to evaluate the primary and long-term results of selective catheter-directed therapy for iliofemoral and high femoral vein thrombosis.

2. Materials and methods

Patients were enrolled in the single center, prospective clinical study between July 1997 and June 2005. Clinical and venographic controls were performed between September 1997 and May 2008 at the radiology and internal medicine wards of our tertiary care center. The study protocol was approved by the institutional review board, and all participants provided written informed consent for the procedure and follow-up.

2.1. Patients

All patients who suffered from acute DVT with symptom duration of less than 2 weeks, diagnosed initially by ultrasound, were candidates for this study. For the selective catheter-directed therapy, patients had venographically confirmed iliofemoral vein thrombosis with or without caval involvement, or severely symptomatic high femoral vein thrombosis with or without popliteal-crural vein involvement and they were considered to tolerate the therapy. The following exclusion criteria were applied: uncontrolable hypertension, stroke within three months, gastrointestinal or other major bleeding within three weeks, and major surgery within 1 week.

During an 8-year period, altogether 70 patients with acute DVT extending to the high femoral or iliac vein were registered for the study. In the initial phase, 4 patients were excluded because they did not strictly meet the study criteria. Additional 10 patients were not considered to tolerate the therapy and catheter-directed thrombolysis was not conducted. Thus, altogether 56 patients with high femoral (16 patients) or iliac vein (40 patients) DVT treated with selective catheter-directed therapy were included in the study. Baseline characteristics of the patients, including factors predisposing to DVT, are shown in Table 1. The most prevalent predisposing factors were the use of contraceptive pills and being positive for heterozygous Factor V Leiden. However, none of the study patients were homozygous for the Factor V Leiden mutation.

2.2. Catheter-directed treatment

Catheter-directed treatments were performed by two interventional radiologists with 2 and 5 years of experience at the beginning of the study. The basic technique of the catheter-directed therapy was selective thrombolysis. Venous access was done by ultrasound guidance. Access sites varied depending on the level and extent of thrombosis. Contralateral femoral vein access was preferred if an iliocaval segment was not involved in the thrombosis. Ipsilateral popliteal or proximal deep crural vein access was used in cases of thrombosis extending up to the proximal common iliac vein or inferior vena cava. In ipsilateral technique a short 6 Fr introducer sheath was inserted into the vein while in the contralateral technique a 45 cm long sheath (Flexor, Cook Inc., Bloomington, IN, USA) was navigated over the cava bifurcation. The A hydrophilic guide wire was navigated through the thrombotic segment and a multiple side hole infusion catheter (Pulse Spray, Angiodynamics, Queensbury, NY, USA) was placed inside the thrombotic segment. Forceful injections of concentrated urokinase (5000 units/mL), up to a dose of 250,000–500,000 units, were performed during the initial intervention, followed by infusions (100,000–240,000 units/h) in the surgical recovery room. Venographic controls were performed every 12–24 h to follow lysis. The techniques included contemporary heparin therapy administrated to a peripheral vein with a target of 2 to 3-fold level of activated partial thromboplastin time (APTT) in comparison to reference values (target 46–99 s). The therapy was continued until anticoagulation reached therapeutic level (INR >2). The APTT/partial thromboplastin time (PTT) and fibrinogen levels were measured every 6 h. Fibrinogen was not allowed to decrease to less than 1 g/L. During the control venography, additional thrombus maceration was routinely performed using balloon angioplasty (Opta Pro, Cordis Europe, LJ Roden, Netherlands) and thrombus aspiration with an 8 Fr PAT-RAT catheter (Angiomed, Karlsruhe, Germany). Stent placement was indicated by residual iliac vein stenosis after PTA and thrombolysis extending to 48 h. The diameter of the PTA balloon was selected to match the size of the vein adjacent to the lesion while the stent was measured to be 2 mm oversized and the length to cover the stenotic segment at least by 2 cm marginal. A temporary or permanent caval filter was placed in cases with recurrent pulmonary emboli or long, free-floating thrombus extending to the inferior vena cava. The subsequent warfarin therapy continued for six months. All patients were treated with compression stockings as standard adjunctive treatment.

2.3. Patient follow-up

Clinical control was scheduled after one week, 1 month, 3 months, 6 months, 12 months, and yearly thereafter. Venography from pedal vein injection was routinely performed at 1–3 months, 6–12 months, and 5–10 years after treatment. The clinical status was reviewed and patient interview performed by a specialist in internal medicine with a focus on the signs and symptoms of PTS, such as pain, swelling, heaviness, cramps, paraesthesiae, itching, teleangiectasia, reticular veins, varicose veins, edema, pigmentation, lipodermatosclerosis, and healed or active leg ulcers. Recurrent DVT and pulmonary embolism were recorded.

2.4. Study endpoints

2.4.1. Primary result

Procedural success upon the completion venography was defined as complete (no visible thrombosis and less than 30% residual stenosis); partial (patent vein but visible thrombosis and/or more than 30% residual stenosis); or failure (no lytic effect after treatment). Procedural complications were classified as major, necessitating active treatment and/or a prolonged hospital stay, and minor, requiring no active therapy [8].