Determinants of Early and Long-term Efficacy of Catheter-directed Thrombolysis in Proximal Deep Vein Thrombosis

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ABSTRACT

Purpose: Catheter-directed thrombolysis (CDT) for proximal deep vein thrombosis (DVT) effectively enhances clot removal and recently has been shown to reduce the development of postthrombotic syndrome (PTS). This study was performed to identify potential markers for early and long-term efficacy of CDT, adverse events, and their interrelationship.

Materials and Methods: Patients aged 18–75 years (mean, 54 y; 33 women) with first-time proximal DVT and symptoms up to 21 days were included in subanalyses in an open, multicenter, randomized, controlled trial. Early efficacy was assessed with a thrombus score based on daily venography. Six-month and 2-year follow-up included iliofemoral patency assessed with duplex ultrasound and air plethysmography, and PTS was assessed with the Villalta scale.

Results: A mean clot resolution of 82% ± 25 was achieved in 92 patients. Successful lysis (ie, ≥ 50%) was obtained in 83 patients. Early efficacy was equal for femoral and iliofemoral thrombus and not related to thrombus load before CDT, symptom duration, or predisposing risk factors. Lower thrombus score at completion of CDT was associated with increased patency at 24 months ($P = .040$), and increased patency after 6 and 24 months was correlated with reduced development of PTS after 24 months ($P < .001$). Bleeding complications were mainly related to the puncture site, and popliteal vein access led to fewer bleeding incidents.

Conclusions: CDT via popliteal access was safe, effectively removed clots, and restored iliofemoral patency. Preprocedure evaluation did not identify patients who did not benefit from treatment. Early efficacy and follow-up patency are of importance to reduce the risk for PTS.

ABBREVIATIONS

CDT = catheter-directed thrombolysis, DVT = deep vein thrombosis, PTS = postthrombotic syndrome

Acute deep vein thrombosis (DVT) of the lower limb is a common disease associated with increased mortality and substantial morbidity (1), with an estimated annual incidence of approximately 1 in 1,000 (2). Current guidelines recommend anticoagulant therapy and use of elastic compression stockings to prevent postthrombotic syndrome (PTS) (3). Despite adequate anticoagulation, which reduces thrombus propagation, embolization, and recurrence, PTS develops in 20%–50% of patients following a proximal DVT—ie, DVT localized in the popliteal vein and above (4)—with approximately 5%–10% of cases being severe. Recent clinical studies suggest that compression therapy may reduce the rate of PTS by approximately 50% (5,6), which substantiates the importance of such preventive measures.

PTS evolves from residual venous obstruction caused by incomplete thrombus resolution causing impaired venous return and/or venous insufficiency caused by destruction of

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vein valves by the thrombus and/or associated inflammatory responses (7). Venous obstruction and insufficiency eventually lead to ambulatory venous hypertension. 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 (8–13), but, until recently, no clinical benefit has been documented in randomized clinical trials, and the 2012 guidelines of the American College of Chest Physicians suggest anticoagulant therapy alone versus CDT (grade 2C recommendation) (3).

The Norwegian Catheter-directed Venous Thrombolysis study reported by Enden et al (14), which was the first randomized, controlled trial with long-term follow-up for evaluation of additional CDT, demonstrated a reduction in the development of PTS. The ongoing North American Acute Venous Thrombosis: Thrombus Removal with Adjunctive CDT (clinicaltrials.gov identifier NCT00790335) and Dutch Catheter versus Anticoagulation Alone for Acute Primary (Ilio)Femoral DVT (clinicaltrials.gov identifier NCT00970619) trials will also assess the efficacy of adjunctive techniques in addition to CDT for thrombus removal. The original CDT procedure is a minimally invasive percutaneous thrombolytic technique whereby a fibrinolytic drug is delivered directly into the thrombus via an intravenous multiple–side hole perfusion catheter.

The overall benefit of CDT depends on various underlying factors that need to be investigated further; including patient selection and technical approach. Predisposing risk factors, symptom duration, and thrombus extension are predefined variables, whereas choice of venous puncture site, adjunctive angioplasty, and total CDT treatment time are matters of debate. Contemporary venous thrombectomy and pharmacomechanical thrombolysis may further enhance thrombus removal and shorten treatment time, possibly at the expense of an increased risk of complications (15,16).

In the present report, we investigate baseline characteristics and technical aspects to identify potential markers for the early and long-term efficacy of CDT, adverse events, and their interrelationship.

MATERIALS AND METHODS

Study Participants

Patients aged 18–75 years with duration of symptoms up to 21 days and a first-time objectively verified iliofemoral or proximal femoral DVT (17) above midthigh level were recruited from 20 hospitals within the Norwegian Southeastern Health Region as part of the Norwegian Catheter-directed Venous Thrombolysis study (14). Patients with increased risk of bleeding or life expectancy shorter than 2 years were excluded. Complete inclusion and exclusion criteria have been published elsewhere (14). After written informed consent was obtained, patients were randomized to receive standard treatment alone or CDT in addition to standard treatment. The study is registered at clinicaltrials.gov with unique identifier NCT00251771; was approved by the Regional Committee for Medical and Health Research Ethics (counterpart of an institutional review board), the Norwegian Medicines Agency, and the Norwegian Data Protectorate; and adhered to the principles outlined in the Declaration of Helsinki.

Procedures

The DVT diagnosis was verified by ultrasound (US) or, if inconclusive, by supplementary venography or computed tomographic (CT) venography. In accordance with local routines based on international guidelines, anticoagulant treatment was initiated the same day with the use of low molecular weight heparin (18). CDT was initiated on the subsequent working day, and low molecular weight heparin therapy was discontinued at least 8 hours before the procedure. A bolus dose of 5,000 IU unfractionated heparin was given at the start of the procedure, followed by an infusion of unfractionated heparin (15 U/kg/h) adjusted to keep activated partial thromboplastin time (Cephotest; Axis-Shield, Oslo, Norway) at 1.2–1.7 times prolongation, ie, 40–60 seconds.

The procedure was performed with the patient in the prone position on the angiography table. After local anesthesia was obtained, a 6-F introducer sheath was inserted into, preferably, the popliteal vein of the affected leg. US guidance was used for all punctures. Other optional puncture sites were the ipsilateral posterior tibial vein and the ipsi- or contralateral femoral vein. The anatomy and the complete extension of the thrombus were then visualized on venography. An appropriate-length perfusion catheter (Uni*Fuse infusion catheter; AngioDynamics, Latham, New York) was inserted with the multiple side holes covering 10–50 cm depending on the length of the thrombotic segments. Catheter-directed infusion of alteplase (Actilyse; Boehringer-Ingelheim, Ingelheim am Rhein, Germany) was then established. Alteplase 20 mg in 500 mL 0.9% NaCl was administered at a steady infusion rate of 0.01 mg/kg/h, with a maximum dose of 20 mg per 24 hours (corresponding to a maximum of 0.83 mg/h) and a non–weight-adjusted dose of 20 mg alteplase per 24 hours for patients larger than 83 kg. The infusion was only briefly discontinued during daily venography performed to monitor the progress of thrombolysis. The thrombolytic agent was given until complete lysis was achieved or venography showed no further improvement, with a maximum duration of 96 hours. Patients were confined to bed during the thrombolytic infusion and monitored in a hematologic ward (13). A thrombectomy device was used in only one patient. Adjunctive balloon angioplasty and insertion of stents were performed at the discretion of the operator to obtain flow and stenosis of less than 50%. No antiplatelet therapy was given. After CDT, all patients received standard therapy with oral anticoagulation for at least 6 months and were