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CLINICAL RESEARCH STUDIES

Residual rates of reflux and obstruction and their correlation to post-thrombotic syndrome in a randomized study on catheter-directed thrombolysis for deep vein thrombosis

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Background: **Deep vein thrombosis (DVT) often results in venous valvular incompetence and incomplete recanalization, followed by post-thrombotic syndrome (PTS). Treatment with additional catheter-directed thrombolysis (CDT) in patients with an iliofemoral DVT has been shown to reduce the frequency of PTS. The objective of this study was to assess the effect of CDT on venous reflux and patency and to identify possible predictors for the development of PTS.**

Methods: **Open, multicenter, randomized, controlled clinical trial. Patients (18-75 years) with a first-time iliofemoral DVT were randomized to receive conventional treatment with anticoagulation and compression stockings or CDT in addition to conventional treatment. Follow-up after 6 and 24 months included ultrasound and air plethysmography for evaluation of venous reflux and patency. PTS was assessed with the Villalta score. Possible predictors of PTS were analyzed in multivariate logistic regression models.**

Results: **Following additional CDT, deep venous reflux was detected in 65.2% (95% confidence interval [CI], 54.8-74.2) of patients at 6 months and 66.7% (95% CI, 56.4-75.6) at 24 months. The absolute risk reduction of deep venous reflux was 11.9% (95% CI, 1.1-24.9) after 6 months and 16.5% (95% CI, 4.2-28.8) after 24 months in the CDT arm compared with controls. Correspondingly, venous patency was regained in 65.9% (95% CI, 55.5-75.0) of patients at 6 months and 74.7% (95% CI, 64.9-82.6) after 24 months. Patency was regained in 18.5% (95% CI, 4.4-32.6) more patients after 6 months and 15.1% (95% CI, 1.8-28.5) more patients after 24 months compared with controls. Independent of treatment allocation, patients with fully recanalized and competent deep veins at 6-month follow-up had a 40.5% (95% CI, 26.4-54.7) absolute risk reduction of developing PTS compared with patients with abnormal vein assessment. Reflux and lack of patency at 6 months were found to be independent predictors of PTS development in patients treated with CDT (odds ratio, 8.3; 95% CI, 2.6-26.8 for patients with reflux, and odds ratio, 0.17; 95% CI, 0.06-0.49 for patients with patency).**

Conclusions: **Additional CDT improved patency and reduced reflux. Both parameters were found to be strong predictors of PTS in patients treated with CDT. Noninvasive vein assessments of patency and reflux may be helpful to identify and monitor patients at high risk of PTS. Our findings provide evidence for the importance of early recanalization with CDT for acute iliofemoral DVT. (J Vasc Surg: Venous and Lym Dis 2014;2:123-30.)**

Acute iliofemoral deep vein thrombosis (DVT) treated with anticoagulant therapy and elastic compression stockings (ECS) often results in a chronic post-thrombotic syndrome (PTS), which is characterized by persistent swelling, pain, and skin changes.[1] PTS is associated with reduced quality of life and increased cost burden.[2] Recently, the Norwegian Catheter-directed Venous Thrombolysis (CaVenT) study demonstrated a long-term clinical benefit in terms of a 15% absolute reduction in PTS development after 24 months in patients with an iliofemoral DVT who were treated with additional catheter-directed thrombolysis (CDT) compared with the standard treatment group who received anticoagulation and compression stockings alone.[3] Iliofemoral patency after 6 months was more often regained in the CDT group, and patency after 24 months correlated to the remaining thrombus load after completed CDT treatment.[4,5]

These findings support the "open vein hypothesis," which postulates that effective removal of thrombus can prevent venous incompetence and/or improve venous patency; the two likely pathophysiologic mechanisms contributing to a persistent venous dysfunction and the development of PTS.[6-9]

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Incomplete recanalization and incompetent vein valves are common following extensive DVT.[10] Case series have indicated improved patency and less reflux after additional CDT treatment,[11] and one randomized clinical trial with 6 months, in addition to the CaVenT study, has reported on improved patency rates after additional CDT compared with anticoagulation alone.[4,12] This limited documentation initiated the CaVenT study, which was the first randomized, controlled trial with long-term and clinically relevant follow-up for evaluation of additional CDT.

The aims of the present report were to assess whether regained venous patency and development of deep venous reflux differed between patients in the CaVenT study treated with additional CDT compared with control patients who received standard treatment alone, and to identify possible predictors of PTS development.

METHODS

Study design and participants

Patients aged 18 to 75 years with a first-time objectively verified iliofemoral or femoropopliteal DVT above mid-thigh level and symptoms up to 21 days were recruited from 20 hospitals within the Norwegian southeastern health region as part of the CaVenT study.[3] This was an open-label, randomized controlled trial. DVT of the lower limb was verified by routine diagnostic work-up using compression ultrasound, venography, or computed tomography if ultrasound was inconclusive. Patients with an increased risk of bleeding or life expectancy shorter than 2 years were not eligible. Complete study design, eligibility criteria, and trial profile have been reported elsewhere.[3,13] In total, 209 patients were randomized to standard treatment with at least 6 months of anticoagulation and 24 months of ECS therapy, or to CDT in addition to standard treatment. The study was approved by the Regional Committee for Medical and Health Research Ethics, the Medicines Agency, and the Data Protectorate, and adhered to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients.

Treatment strategies

Anticoagulation treatment was initiated on the day of diagnosis according to local routines. Based on international guidelines, low-molecular-weight heparin (LMWH) was administered followed by oral warfarin until target international normalized ratio (INR) of 2.0 to 3.0.[14] Patients allocated CDT treatment did not receive warfarin initially and were transferred to one of four interventional centers, where thrombolysis was initiated on the first following working day. LMWH therapy was discontinued at least 8 hours prior to the procedure. At the start of the procedure, a bolus dose of 5000 IU unfractionated heparin was given, 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 to 1.7 times prolongation (ie, at 40-60 seconds).

Following a local anesthetic, a 6-F introducer sheath was inserted, guided by ultrasound, preferably, in the popliteal vein of the affected leg. A venography was performed to visualize the complete extension of the thrombus, and a perfusion catheter (Uni*Fuse Infusion Catheter; Angiodynamics, Latham, NY) was inserted with the multiple side holes covering 10 to 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. Twenty milligrams alteplase in 500 mL 0.9% NaCl was administered at an infusion rate of 0.01 mg/kg per hour; maximal dose 20 mg/24 hours. Patients were confined to bed during the thrombolytic infusion and monitored in a hematological ward.[13] Progression of the thrombolysis was assessed by daily venography and continued until complete lysis or no further improvement and a maximum of 96 hours.[4]

Adjunctive balloon angioplasty and insertion of stents were performed at the discretion of the operator to obtain flow and <50% stenosis. Dilatation with balloon angioplasty only was performed in 24 (26.7%) of the patients treated with additional CDT, 16 were in the femoral vein. Wallstents (average diameter, 15.7 mm [range, 12-18 mm]; Wallstent; Boston Scientific, Natick, Mass) were inserted in the iliac veins of 16 CDT-treated patients (17.8%). Five of these patients were identified with May-Thurner syndrome and treated with adjunctive angioplasty: two with a balloon only and three with stents.[5] No antiplatelet therapy was given. A weight-adjusted full therapeutic dose of subcutaneous LMWH twice daily was started 1 hour after removal of the CDT catheter. Oral anticoagulation with warfarin for at least 6 months was then established according to guidelines. Three major bleedings were reported in the CDT group. There were no deaths, pulmonary embolisms, or cerebral hemorrhages related to CDT. There were no bleeding complications in patients allocated to control during the same period.[3]

In the conventional treatment arm, oral anticoagulation was initiated immediately after randomization. All patients in both treatment arms were advised to wear knee-high ECS class II daily for at least 24 months.

Noninvasive vein assessments

Clinical follow-up visits at 6 and 24 months included ultrasound and air plethysmography (APG) and were performed by one experienced vascular physiologist (C.S.) who was unaware of treatment allocation.

Using an ultrasound scanner (Logiq E9; GE Healthcare, Chalfont St. Giles, UK) with a 9L, broad-spectrum linear transducer, frequency range 2 to 8 MHz, the examination was performed with the patient standing, and an automated pneumatic cuff was placed distally to the segment to be examined. Grayscale compression ultrasound assessed compressibility of the femoral vein. Doppler ultrasound was used to evaluate iliofemoral venous flow and venous reflux. A compression unit enabled instantaneous inflation and deflation (VenoPulse; STR Teknikk, Ålesund, Norway), ensuring a standardized repeatable