Treatment of Chronic Deep Vein Thrombosis Using Ultrasound Accelerated Catheter-directed Thrombolysis

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WHAT THIS PAPER ADDS
Few data are available concerning the feasibility, safety, and efficacy of ultrasound-accelerated, catheter-directed thrombolysis (UACDT) in "chronic" lower extremity deep vein thrombosis. Our study illustrates the beneficial role of UACDT using the EkoSonic system. Importantly, the study showed a higher treatment success rate with significant reduction in thrombolytic duration, thrombolytic dosage, and hemorrhagic complications. Additional clinical studies are necessary to validate the benefit and corroborate our results.

Objective: To evaluate the feasibility, efficacy and safety of ultrasound-accelerated catheter-directed thrombolysis (UACDT) in the delayed treatment of lower extremity deep venous thrombosis (DVT).

Design: Twelve patients with unilateral iliofemoral or femoropopliteal DVT (mean symptom duration 92 ± 44 days) were prospectively investigated.

Method: UACDT was performed using recombinant human tissue plasminogen activator delivered using the EKOS EkoSonic system. Stents were deployed if indicated by post-procedure venography. Follow-up comprised weekly duplex ultrasound for 1 month and monthly thereafter.

Results: Successful thrombolysis occurred in 11/12 limbs (92%; complete 6/12, partial 5/12) after a mean infusion time of 26 ± 7 hours. 2/12 patients required angioplasty and stent insertion. At a mean follow-up of 9 (6–15) months, 10/11 (91%) veins were patent whereas 1/11 re-occluded at 2 months (patient with protein-C deficiency). 2/11 limbs developed symptoms/signs of post-thrombotic syndrome and 3/11 had developed deep vein reflux (duplex ultrasound). 2/12 patients experienced peri-catheter bleeding but no major hemorrhage or symptomatic pulmonary embolism occurred.

Conclusions: This preliminary evidence suggests that UACDT may be a safe and effective option for the delayed treatment of lower limb DVT.

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INTRODUCTION
Deep venous thrombosis (DVT) of the lower extremity is recognized as a cause of both pulmonary embolism (PE) and the post-thrombotic syndrome (PTS).1 Although anti-coagulation is currently considered the standard of care to prevent PE and recurrent DVT, it remains ineffective in removing thrombus burden and consequently does not prevent PTS, which can appear months to years after an acute DVT.2

A novel technique, ultrasound-accelerated catheter-directed thrombolysis (UACDT), has been developed to rapidly and completely lyse existing thrombus, thereby decreasing the potential risk of PTS.3,4 The mechanism proposed is that this technique integrates high-frequency, low-intensity ultrasound (US) with standard catheter-directed thrombolysis (CDT) in order to accelerate clot dissolution, reducing treatment time, drug dosage, and the incidence of thrombolysis-related complications. US waves are known to increase permeability of biological structures including tissue, vessel walls, and thrombus. This increased permeability combined with the pressure gradient associated with an acoustic field is thought to facilitate delivery of therapeutic agents into, and past, older organized thrombus into regions where dissolvable clot remains.5,6

Several studies demonstrate evidence of safety and effectiveness in removing acute venous thrombosis using EKOS,7–9 but limited data are available supporting its use for chronic DVT, particularly in patients with long-standing symptoms. Treatment of chronic DVT has long been a clinical problem as the thrombus has a tendency to adhere and organize after the acute stage. Therefore, the aim of this

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study is to examine the feasibility of using UACDT as a safe and effective option to treat patients with chronic DVT defined as having symptoms for greater than 28 days.

METHODS

Study patients

Between September 2009 and October 2011, 21 consecutive patients who had a first episode of proximal DVT were considered for this prospective study. Patients with chronic lower extremity DVT were eligible. The diagnosis of DVT was confirmed by duplex ultrasound (DUS) and venography. For this purpose, a Toshiba Xario SSA-660A series (Toshiba Medical System Corporation, Nasu-Tokyo, Japan) color Doppler ultrasound system was used with a 4.8–11 MHz (Toshiba PLT 704 AT) linear transducer. Proposed exclusion criteria included isolated infrapopliteal thrombosis, recurrent ipsilateral DVT, pre-existing leg ulcers, a short life expectancy or contraindications to anticoagulation, contrast media, and thrombolytic agents. Contraindications to thrombolytic agents were considered to be active internal bleeding, recent cerebrovascular accident, allergy to thrombolytic agents, recent major surgery, recent serious gastrointestinal bleeding, recent serious trauma or pregnancy. Computerized tomography angiography (CTA) was used to exclude subclinical pulmonary embolism, prior to the UACDT in all patients. Informed consent for participation in the study was obtained according to the guidelines of our institutional review board and the local ethics committee, which approved the study.

Treatment procedure

The procedures were performed in a hybrid vascular operating room. Patients were positioned prone and the popliteal vein was catheterized with a 6 F micro access set under DUS guidance using a 21 G needle and a 0.46 mm diameter guide wire after which ascending venography was performed. UACDT was performed using the EKOS EkoSonic Endovascular System (EKOS Corporation, Bothell, WA, USA).

A 5.4 F multi-lumen drug delivery catheter and matching US coaxial core wire are provided by the manufacturer with treatment zone lengths varying between 6 and 50 cm (Fig. 1). The drug delivery catheter was navigated over a 0.035 inch guide wire so that the treatment zone traversed the entire clot and the tip exited the thrombus. After final positioning, the guide wire was exchanged for a matching US core wire containing a series of US transducer elements (2.2 MHz, 0.45 W) distributed approximately 1.0 cm apart to evenly deliver US energy radially along the distal coaxial infusion zone. After priming the drug lumens of the catheter with sub-therapeutic unfractionated heparin (1,000 U/mL), continuous infusion of the thrombolytic agent was initiated through the side-holes along the treatment zone of the UACDT infusion catheter. A recombinant human tissue plasminogen activator (tPA), Alteplase (Actilyse, Boehringer Ingelheim GmbH, Germany), was given in a 5 mg bolus followed by an infusion at 0.02 mg/kg/hr during the treatment. US energy was initiated via the core wire, simultaneously with the infusion of the tPA. The system control unit, which monitors temperature and power in the infusion zone via a series of thermocouples in the catheter, automatically adjusted power to optimize lysis of the treated segment.

We made the decision of when to stop thrombolytic therapy based on each patient’s disease and anatomy, graphical information displayed on the ultrasound system control unit and control venographies taken. We stopped UACDT when we transferred a patient to the angiography suite. Venography was performed before removing the introducer to determine whether there was recanalization of the treated vein. If we did not believe that recanalization of the target vessel was adequate at venography, we then reinserted the drug delivery catheter back into the target vessel and continued the UACDT for an additional 12 hours. If the patient had chronic DVT, if the length of occlusion was long or if the patient had a very large thrombus burden, we performed thrombolytic treatments for as long as 39 hours.

After thrombolysis, further adjunctive procedures consisting of PTA and stent placement were performed if there was an underlying iliac vein stenosis >50%.

Warfarin sodium was routinely started prior to hospital discharge and this was continued for at least 6 months, with the dose adjusted to maintain an international normalized ratio (INR) of 2.0–3.0. Adjuvant elastic compression therapy was recommended and encouraged for more than 1 year.
Assessment of venous recanalization and symptoms resolution

Venous recanalization after completion of treatment was determined by comparing the thrombus scores of the pre- and post-treatment venograms, which was categorized as “complete” recanalization for 95—100% restoration of patency, “partial” for 50—95% and “minimal” for less than 50% as a result of residual stenosis or organized thrombus. The final score was calculated as the percentage difference between pre- and post-treatment venograms. Relief of symptoms (pain and swelling) at the completion of treatment was rated as (i) absent, (ii) poor, (iii) significant, or (iv) complete. Clinical success was defined as achieving at least 50% thrombus resolution and immediate clinical improvement of symptoms defined as resolution of pain or swelling following thrombolysis.

Follow-up

After hospital discharge, all patients were followed in the outpatient clinic, weekly during the first month and then at monthly intervals. At each visit, every patient underwent a clinical evaluation according to a modified Villalta scale and a DUS assessment of the affected lower limb for patency of the deep venous system and presence or absence of residual thrombus in the treated veins as well as venous reflux. The presence of five leg symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and six objective signs (pretilial edema, skin induration, hyperpigmentation, new venous ectasia, redness, and pain during calf compression) were scored. Each of the symptoms and signs were rated as 0 (absent), 1 (mild), 2 (moderate) or 3 (severe). Clinical evaluation outcomes were classified as follows: a total score greater than 14 points or a venous ulcer was defined as severe post-thrombotic syndrome (PTS); 5—14 points was considered to indicate mild PTS, and less than 5 points was given for no PTS. Post-treatment DUS assessment of the affected lower limb was also performed at weekly intervals for 1 month, and monthly thereafter. Valvular reflux was defined as greater than 0.5 seconds for the valve closure time after distal compression and release using an ultrasonic probe with the patient standing and non-weight bearing on the treated limb. Primary patency was defined as confirmed patency and <50% restenosis at the sixth month as documented by DUS. We recorded limb circumferences in the thigh at 15 cm above the knee joint and in the calf at 10 cm below the tibial tuberosity prior to treatment and at the 6-month post-treatment review.

Complications

Complications were classified according to scoring system of the Society of Interventional Radiology. Complications not requiring therapy and presenting without consequence or complications requiring nominal therapy and without a consequence, including an overnight admission for observation, were considered “minor”.

RESULTS

Patients

Of the 21 patients evaluated, nine were excluded because of previous ipsilateral DVT (n = 3), pre-existing leg ulcers or venous insufficiency (n = 2), poor life expectancy (n = 1), recent cerebrovascular accident (n = 1), or inability to participate at follow-up visits (n = 2). The remaining 12 patients were enrolled in this study. Their baseline characteristics are shown in Table 1. Mean total alteplase dose was 42.4 ± 7.9 (range 30—54) mg and the mean infusion time was 26.2 ± 7.0 (range 16—39) hours. The location of thrombosis was in the iliofemoral segment in five patients and the femoropopliteal segment in seven patients. The drug delivery catheter was successfully positioned within the occlusions and UACDT was successfully performed in all patients. There were no device failures or adverse events associated with the EKOS system. Thrombolysis was successful in 11 of 12 patients (92%) with complete clot lysis (>95% restored patency) in six patients and partial clot lysis (50—95% restored patency) in five patients. In one patient presenting with 154 days since onset of symptoms, thrombolysis was not successful with only minimal clot lysis (<50%). Figs. 2 and 3 illustrate representative cases. A statistically significant correlation was found between the percentage of thrombus removal and degree of clinical improvement (p < .01, Table 2). Two patients treated for iliofemoral DVT showed symptoms of associated iliac vein stenosis and were further treated to improve flow with balloon angioplasty and stent implantation (60/16 mm Wallstent, 40/10 mm Nitinol stent and 100/14 mm Wallstent, respectively) immediately after control venography (Fig. 3).

Immediate clinical improvement was observed in 11 of 12 patients, with significant or complete clinical improvement occurring in 10. These patients also exhibited over 50% of thrombus clearance. All together, clinical success was observed in 10 patients (83%). In the follow-up period, thigh circumference of the affected limb decreased by 3.9 ± 1.7 cm, and calf circumference decreased by 3.3 ± 1.5 cm in the first month (Table 3).

Table 1. Patients’ baseline characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tr>
<td>Age (year, range)</td>
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</tr>
<tr>
<td>Gender (female/male)</td>
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</tr>
<tr>
<td>Reported symptom duration (days, range)</td>
<td>92.4 (34—183)</td>
</tr>
<tr>
<td>Affected limb (left/right)</td>
<td>8/4</td>
</tr>
<tr>
<td>Thrombosis location</td>
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<td>Iliofemoral</td>
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</tr>
<tr>
<td>Femoropopliteal</td>
<td>7</td>
</tr>
<tr>
<td>Risk factors</td>
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<tr>
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<td>4</td>
</tr>
<tr>
<td>Malignancy</td>
<td>2</td>
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</tbody>
</table>
Complications

Bleeding at the catheter insertion site occurred in two patients (17%). The bleeding was controlled in both cases by simple elevation of the limb and application of a compressive bandage, without requiring transfusion or interruption of the procedure. A further patient experienced hematuria after 34 hours on alteplase, with spontaneous remission after interruption of lytic infusion. No patient suffered from serious complications.

Follow-up

The follow-up duration for the 11 patients successfully treated with UACDT was 6–15 (mean 9) months with 10 limbs (91%) still patent at 270 days post procedure, as determined by DUS. One patient with protein-C deficiency, who achieved complete lysis, experienced re-occlusion 2 months after treatment. Primary patency was observed in the remaining 10 patients. Two of the 12 limbs (18%) developed mild PTS that mainly presented as pain, heaviness, and edema of the affected limbs after activities. Mild pruritus was also present in three limbs, but none of these had severe PTS. The median total PTS score was 4 (range 0–9), and seven limbs (64%) had a score <3. Valvular reflux occurred in three (27%) limbs and valvular function was normal in eight patients, as observed with DUS.

DISCUSSION

The goal in treating chronic DVT is to restore flow by adequately recanalizing the obstructed venous segment and to maintain its patency, thus minimizing the risk and severity for PTS. The current study demonstrates the promise for UACDT to achieve early and late success with evidence of effective recanalization and rapid resolution of pain and swelling and persisting patency and absence of reflux at follow-up in this small group of patients with chronic thrombosis. There was also a low rate of bleeding complications. The results contrast with those associated with conventional therapy of anticoagulation with heparin then warfarin, where recanalization depends solely on the endogenous fibrinolytic system. PTS has been reported to develop in 20–50% of these patients within 1–2 years, of which 5–10% develop severe PTS. Results also

Figure 2. (A) Images from a 34-year-old woman who presented with non-acute left lower extremity DVT. The duration of thrombotic occlusions was 34 days. (B) EKOS catheter with a 50 cm treatment length was placed into the thrombus. (C) Follow-up venogram shows complete resolution of thrombus after 24 hours infusion. (D) No underlying stenosis.

Figure 3. Venograms exhibiting complete thrombolysis of left femoro-popliteal vein, as well as the underlying focal stenosis of the left common iliac vein, treated with angioplasty and stent placement. The duration of thrombotic occlusions was 76 days. (A) With the patient in prone position; ascending venogram demonstrated heavy thrombus burden extending into the common femoral vein. (B) After 23 hours of UACDT, flow was restored within the femoro-popliteal vein. (C) However, a focal stenosis (arrow) within the left common iliac vein was observed. (D) Iliac stenosis was treated with angioplasty and stent placement. (E) Final venogram showing complete restoration of flow in the left common iliac vein.
compared favorably with standard CDT where a bleeding rate of 30% has been calculated from pooled data.\textsuperscript{18} Mewissen et al.\textsuperscript{3} reported that treatment with catheter-directed urokinase for a mean of 53 hours in 473 DVT patients resulted in complete thrombus clearance in only 31% of the patients, with bleeding complications seen in 27% including 11% with major bleeding.

These results appear to justify UACDT use with the EkoSonic endovascular system, which combines high-frequency, low-power US with simultaneous catheter-directed thrombolytics to accelerate clot dissolution. It is postulated that it acts by first disassociating the fibrin mesh to increase permeability of the thrombus, making plasminogen receptors available to the thrombolytic agent. At the same time, acoustic microstreaming caused by the US wave pressure is believed to drive the thrombolytic agent away from the catheter deep into the loosened thrombus.\textsuperscript{19} Motarjeme\textsuperscript{40} and Parikh et al.\textsuperscript{21} were the first to report use of UACDT in DVT. They reported significantly higher complete clot lysis rates with UACDT compared with standard CDT, without raising bleeding or thromboembolic risk. UACDT is reported to be effective also for treating peripheral arterial occlusions, massive PE,\textsuperscript{22} and acute ischemic stroke.\textsuperscript{23}

The primary limitation of the current study is the small patient population of only 12 patients. Clearly, additional clinical studies will be necessary to further validate the benefits and corroborate our results. Although the mean clinical follow-up time at 9 months may be insufficient to observe late changes related to PTS such as cutaneous hyperpigmentation and phlebopathic ulcers, we believe it is adequate to assess early signs of venous insufficiency. We recognize that defining chronicity of thrombus based solely on the age of symptoms may not be adequate when making clinical decisions. We believe that the location of thrombus, its consistency, medical therapy initiation time, use of compression stockings, dose of anticoagulation medication, and other factors may also play a role in successful clinical outcomes. A more reliable classification of clot age is necessary but is beyond the scope of this study.

In summary, our study suggests that UACDT using the EkoSonic system can produce a higher treatment success rate with significant reduction in thrombolytic duration, thrombolytic dosage, and hemorrhagic complications when treating chronic lower extremity DVT than other forms of treatment.

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CONFLICT OF INTEREST

All authors declare that there is no conflict of interest and disclose any financial and personal relationships with other people or organizations that could inappropriately influence this study.

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REFERENCES


