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Safety and Feasibility of Ultrasound-accelerated Catheter-directed Thrombolysis in Deep Vein Thrombosis

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Abstract *Objective:* One in four patients with primary iliofemoral deep vein thrombosis (DVT) develops post-thrombotic syndrome (PTS) within 1 year despite optimal standard anticoagulant therapy. Removal of thrombus by thrombolytic drugs may prevent PTS. The aim of this study was to assess the short-term safety and efficacy of ultrasound-accelerated catheter-directed thrombolysis (US-accelerated CDT).
Design: This was a prospective non-randomised interventional study with US-accelerated CDT for DVT.
Patients and methods: Twelve patients with DVT (seven caval–iliofemoropopliteal, three iliofemoropopliteal, one femoropopliteal and one superior caval vein thrombosis) receiving standard anticoagulant and compression therapy, were treated with additional US-accelerated CDT (13 procedures) using the EKOS Endowave® system (EKOS Corporation, Bothell, WA, USA) between October 2008 and January 2010.
Results: Thrombolysis was successful in 85% (11/13), with complete clot lysis (>90% restored patency) and in one case with partial clot lysis (50–90% restored patency). No pulmonary embolism and one bleeding at the catheter-insertion site were observed. In three patients, underlying lesions were successfully treated with balloon angioplasty and stent insertion. Four patients developed early recurrent thrombosis due to untreated residual venous obstruction.
Conclusion: US-accelerated CDT is a safe and promising treatment in patients with DVT. Residual venous obstruction should be treated by angioplasty and stent insertion to avoid early re-thrombosis.

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Patients with acute deep vein thrombosis (DVT) are treated with anticoagulation, compression therapy and mobilisation.[1] This standard DVT tripletherapy decreases mortality by preventing life-threatening pulmonary embolism (PE) and propagation of thrombosis, but has no direct thrombolytic effect. Re-canalisation and the preservation of valve function, therefore, depend on the effectiveness of the patient's own fibrinolytic system. This has resulted in high morbidity due to post-thrombotic syndrome (PTS).

Meissner et al. have demonstrated that valve function is more likely to be retained after early clot lysis.[2] Singh et al. have revealed that the combination of obstruction and reflux, rather than either one of these, significantly increases the risk of developing PTS.[3] Rapid clot dissolution by early catheter-directed thrombolysis (CDT) before the onset of valvular damage is suggested to be a way to prevent the development of PTS.

A number of methods of CDT are currently available for the treatment of DVT as outlined in a recent publication from Pianta and Thomson.[4] Motarjeme[5] and Parikh et al.[6] were the first to report ultrasound-accelerated (US-accelerated) CDT in DVT. They report significantly higher complete clot lysis rates with US-accelerated CDT compared with standard CDT,[7] without raising bleeding or thromboembolic risk. *In vitro* studies have demonstrated that high-frequency, low-power microsonic energy improves lysis of the thrombus considerably by increasing the uptake and penetration of thrombolytic drugs into the thrombus.[8,9] US-accelerated CDT is effective in the treatment of peripheral arterial occlusions,[5] massive PE[10] and acute ischaemic stroke.[11,12] Therefore, US-accelerated CDT may also be a safe and promising candidate for immediate treatment of DVT, having the benefits of thrombolysis combined with minimising potential side effects. Few data are available concerning the feasibility, safety and efficacy of US-accelerated CDT. Therefore, the aim of this study is to confirm prospectively the short-term feasibility, safety and efficacy of additional US-accelerated CDT in patients with DVT treated using standard DVT therapy.

Materials and Methods

Patients

Between October 2008 and January 2010, 12 patients (seven M: five F; median age 44 years (range 5–79)) with symptomatic, duplex and computed tomography (CT)- or magnetic resonance (MR) angiography confirmed DVT and a life expectancy exceeding 6 months were treated with US-accelerated CDT at the University Medical Centre Maastricht (MUMC+, the Netherlands), the University Hospital RWTH Aachen (Germany) and the VU Medical Centre Amsterdam (VUmc, the Netherlands). In five patients, pulmonary embolism, which was confirmed by CT-angiography, was present before the US-accelerated CDT was commenced. One patient developed recurrent thrombosis 4 days after initial successful thrombolysis and received a second thrombolytic procedure. Therefore, 13 cases of US-accelerated CDT were evaluated. Six patients had a recurrent DVT. Exclusion criteria for US-accelerated CDT were gastrointestinal bleeding or a cerebrovascular haemorrhage in the previous year, severe hypertension (>180/100 mm Hg), active malignancy, surgery in the previous 6 weeks and/or pregnancy. In one case of upper-extremity thrombosis, the innominate vein was also involved. The 12 remaining cases involved lower-extremity DVT. In those, the proximal end of the thrombosis reached into the vena cava inferior in eight, the iliac vein in three and the femoral vein in one case. The age of the thrombus (defined as the number of days between the onset of symptoms and the intervention) was 0–6 days (3/13), 7–13 days (5/13), 14–20 days (1/13) or $\geq$ 21 days (4/13) (Fig. 1).

Eligible patients received US-accelerated CDT with recombinant tissue plasminogen activator (rtPA) (10/13) or urokinase (3/13) combined with standard DVT therapy. Anticoagulation was given according to international guidelines (American College of Chest Physicians, 2008) with the duration of planned treatment being 6 months for idiopathic DVT and 3 months for provoked DVT.[1] We received approval or gained exemption for the collection of data without patient identification from the institutional review boards of the MUMC+, the University Hospital RWTH Aachen and the VUmc Amsterdam.

US-accelerated CDT

US-accelerated CDT was performed using the EKOS Endowave® system (EKOS Corporation, Bothell, WA, USA), which combines a targeted-drug-delivery catheter with high-frequency, low-power US energy (Fig. 2). This system uses a standard 0.035-in. guide wire to position the 5.2-F multi-lumen Intelligent Drug Delivery Catheter and matching US coaxial core wires (with available treatment lengths ranging from 6 to 50 cm) across the length of the target clot. In all cases, the procedure was performed in an interventional radiology suite. A 7-F sheath and a 0.035-in. hydrophilic guide wire (Terumo Corporation, Shibuya-ku, Tokyo, Japan) were placed with the assistance of US-guided popliteal, femoral or jugular venous puncture. The catheter was positioned along the guide wire using X-ray guidance, with the end of the catheter at the proximal end of the thrombus. The guide wire was then pulled out and replaced by the Microsonic core containing a series of US transducer elements (2 MHz, 0.45 W) distributed approximately 1.0 cm apart along its leading tip to deliver evenly US energy radially along the coaxial infusion zone.

Thrombolysis

After priming the drug lumens of the catheter with heparin (1000 IU), a single bolus of rtPA (5.0 mg) or urokinase (500,000 IU) was administered by slow infusion. Afterwards, continuous infusion of rtPA or urokinase was initiated through the side-hole-delivery infusion catheter at a mean rate of 1.0 mg h^{-1} rtPA or 100,000 IU urokinase, respectively. Simultaneously, normal saline solution was infused as coolant through the central lumen of the catheter at a rate of 35 ml h^{-1}. Thus, US energy was delivered through the core wire with simultaneous infusion of the thrombolytic drug. All patients were treated with an additional continuous intravenous infusion of heparin through the introducer sheath, which was monitored by assessment of

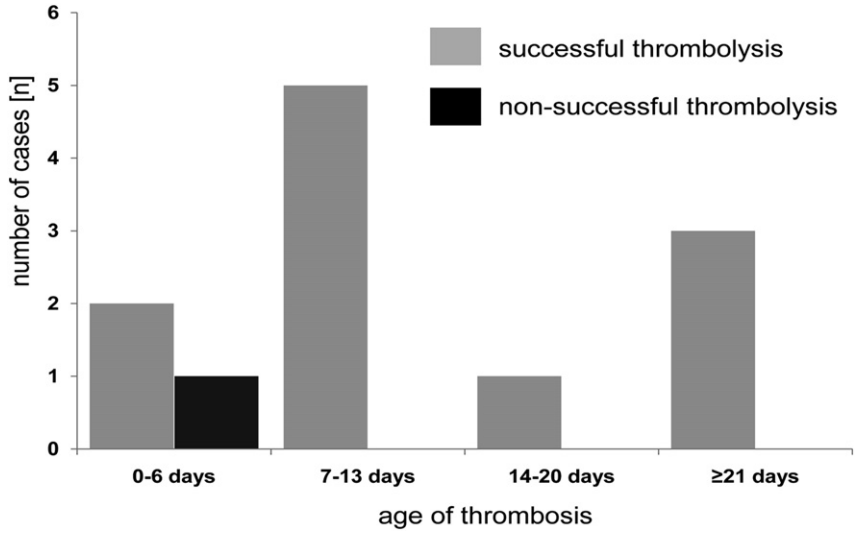

Figure 1 Age of thrombus versus success of thrombolysis This diagram shows there was no relation between the age of the thrombus and the success of thrombolysis in this patient series. Successful thrombolysis includes complete and partial clot lysis, defined as >90% and 50—90% restored venous patency respectively.

the activated partial thromboplastin time (aPPT). Heparin dosage was adjusted to obtain an aPTT ratio of 1.5—2.5. Follow-up phlebograms were performed on all patients the next day and at 24-h intervals thereafter.

Thrombolysis was terminated, if complete clot lysis was achieved or the maximum infusion period of 72 h was reached. Hourly and total infused rtPA and urokinase doses and infusion times were recorded; additional angioplasty with or without stent insertion was performed to treat underlying lesions after thrombus lysis had been achieved. Patients received their thrombolytic care at an intermediate care unit and remained hospitalised for one night after termination of thrombolytic treatment, if no complication arose. After discharge, patients were followed up according to the international guidelines for DVT therapy (ACCP 2008).[1]

Definitions

Thrombolysis success

Complete clot lysis was defined as >90% lysis (restored patency), and partial clot lysis as 50—90% lysis (restored patency) of the initial thrombus, as assessed on the final phlebograms before additional procedures.

Bleeding

Bleeding was classified as major, if it was overt with a fall in haemoglobin of $\geq$2 gd^{-1}, or when haemorrhage led to transfusion of $\geq$2 units of packed red blood cells (RBCs) or whole blood. Bleeding situated in a critical organ (intracranial, retroperitoneal or pericardial) or, if it contributed to death, was also defined as a major bleeding. Bleeding was classified as minor, if it was situated near the catheter-insertion site.

Follow-up

Every 3 months after discharge, all patients returned to the outpatient department for a follow-up visit, including clinical investigation and duplex ultrasound examination to assess the patency of treated vein segments and the extent of post-thrombotic damage to the deep veins of the lower limb.

Results

Successful thrombolysis

Percutaneous catheterisation was successful in 12 procedures, and, in one case, catheterisation of the popliteal vein was achieved by open access.

Eleven out of 13 procedures (85%) resulted in complete clot lysis (>90% restored patency). In one case, only partial clot lysis (50—90% restored patency) was achieved. In one case, thrombolysis was not successful.

The unsuccessful case involved a 5-year-old boy. He developed DVT and PE as the consequence of a previously undetected thrombophilia (Factor V Leiden) and immobilisation with a bilateral long-leg spica cast after orthopaedic surgery.

Fig. 1 shows the age of the thrombus and the success of thrombolysis. In this small study, no relationship was observed between successful thrombolysis and thrombus age.

Immediate adjunctive procedures

In three cases, underlying iliac vein stenosis was diagnosed and successfully treated with balloon angioplasty and stent insertion (60/16 mm Wallstent®, 40/10 mm Nitinolstent® and 100/14 mm Wallstent®, respectively) immediately after thrombolysis. Fig. 2 shows the pre-, intra- and post-thrombolysis phlebograms and the angioplasty with stent insertion of one case involving a 36-year-old female patient with iliocaval vein thrombosis.

Early recurrent thrombosis occurred in four cases of which three were due to inadequate or no treatment of a May—Thurner syndrome (common iliac vein stenosis) demonstrated after completion of thrombolysis.

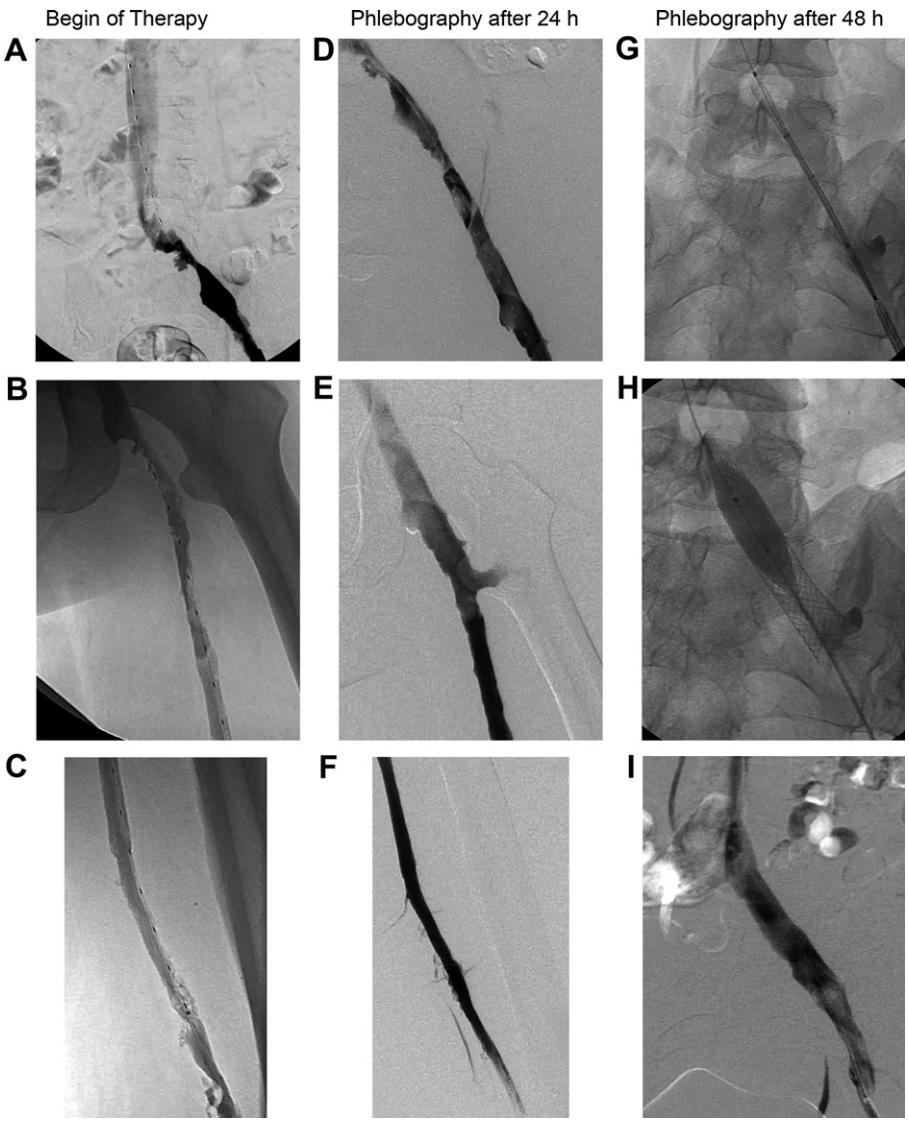

Figure 2 Pre-, intra-, post-thrombolysis and additional balloon angioplasty with stent insertion phlebograms Phlebographic images from a 36-year old female patient who presented with a post-partum thrombosis from the femoral vein up to the inferior caval vein (A—C). Follow-up phlebogram after 24 h US-accelerated CDT, showing a May—Thurner Syndrome (D.) and recanalised iliac vein (D) and femoral Vein (E). After balloon angioplasty a Wallstent® (diameter 16 mm, length 60 mm) was employed to maintain patency of the treated vein (G—I).

The first case involved a 17-year-old female patient, who developed a haematoma at the catheter-insertion site, achieved by open access, and in the calf muscle, during thrombolysis, necessitating a 50% reduction in the hourly thrombolytic drug dose. Although the dose was reduced, successful thrombolysis was achieved. Recurrent thrombosis occurred within a day due to a diagnosed but not immediately treated May—Thurner syndrome. The thrombolytic therapy was not recommenced because of the bleeding complication.

In the second case, which involved a 51-year-old male patient, recurrent thrombosis developed 4 days after initial, successful US-accelerated thrombolysis in whom the iliac stenosis was not treated immediately. Thrombolysis was repeated with success, followed by angioplasty and stenting of the underlying May—Thurner syndrome and the construction of an arteriovenousfistula in the common femoral vein.

In the third case, a 43-year-old male patient, recurrent thrombosis occurred 1 day after successful thrombolysis, in whom an underlying left-sided May—Thurner syndrome was identified and inadequately treated with angioplasty alone without stent placement.

In the fourth case, which involved a 52-year-old female patient, recurrent thrombosis occurred 14 days after successful US-accelerated CDT. This patient had a heparin-induced thrombocytopenia (HIT type II) caused by enoxaparin (Clexane).

Short-term follow-up

The mean follow-up period was 7 months (range 3—17). In this period, no further occlusion of the venous system occurred in the patients, who were discharged with a patent venous system. In the 5-year-old boy with unsuccessful

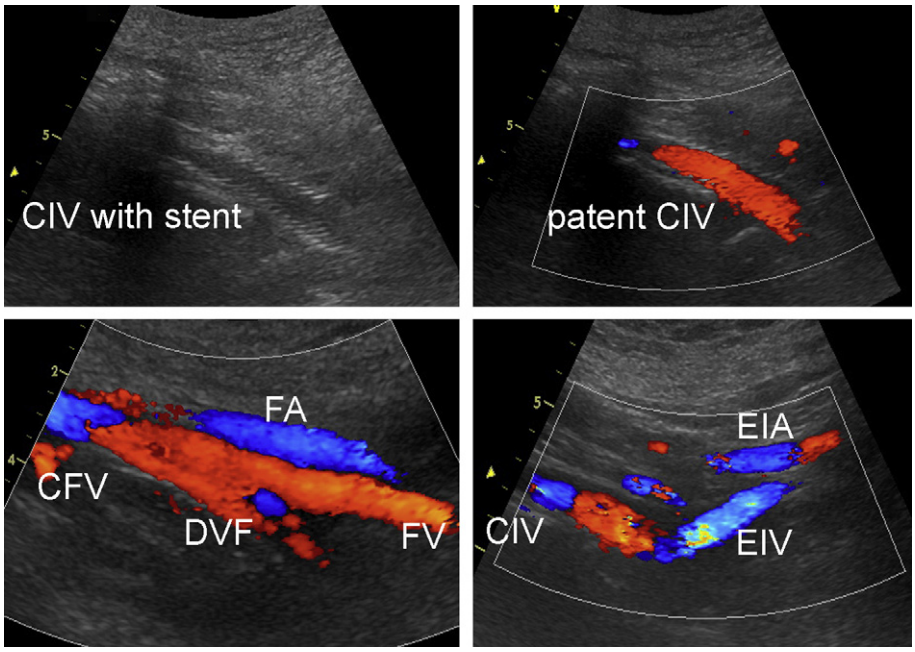

Figure 3 Duplex images at 3-month follow-up of case presented in Fig. 2 The iliac vein with stent and femoral vein remained patent at 3-month follow-up. (CIV = common iliac vein, EIV = external iliac vein, CFV = common femoral vein, FV = femoral vein, FA = femoral artery, DFV = deep femoral vein).

thrombolysis, the 3- and 6-month US follow-up revealed (spontaneous) re-canalisation of the inferior vena cava up to the origin of the left renal vein. The iliac vein remained occluded. In this patient, hypoplasia of the inferior vena cava or a previous DVT probably caused failure of treatment.

In the 17-year-old girl with the untreated reocclusion due to a bleeding complication and a May—Thurner syndrome, 50% re-canalisation of femoral and iliac vein was found after 6 months. Because she suffered from severe venous claudication, the partially recanalised iliac vein was successfully dilated and stented. Fig. 3 shows the duplex images at 3 months of the case presented in Fig. 2.

The patient, who developed a reocclusion due to HIT type 2, displayed 50% re-canalisation of the common iliac and femoral veins at 6 months' follow-up.

The iliac veins of the patient with the early reocclusion after thrombolysis and angioplasty without stent placement remained occluded during follow-up.

Complications

One (1/13; 8%) bleeding complication occurred at the site of the catheter-insertion and in the calf muscle. NoPE was diagnosed during or after the treatment. However, early re-thrombosis was observed in four cases: one due to a HIT type II and three due to an inadequate treatment of residual venous obstruction.

Discussion

Standard DVT treatment focusses on adequate anti-coagulation to prevent PE and thrombus propagation. However, anticoagulation alone has no direct thrombolytic effect. As a result, current DVT treatment often does not restore venous patency, and venous valves are permanently damaged. In addition, underlying venous stenoses such as May—Thurner syndrome, which predispose to recurrent thrombosis, are left untreated. The combination of venous obstruction and reflux significantly increases the risk of developing PTS.[3] Therapy, which can remove the thrombus and restore venous patency, may prevent recurrent thrombosis and PTS.

Our study confirms the promising results of CDT for the treatment of DVT. Most evidence regarding CDT for the treatment of DVT is derived from patient series without controls[5,6,13] or cohort studies,[7,14] and little evidence is available from randomised clinical trials.[15,16] Our study obtained a 92% success rate and highlights the feasibility and capability of the US-accelerated CDT. We observed no PE in our patients during thrombolysis. Bleeding at the catheter-insertion site occurred in one case in whom catheterisation of the popliteal vein was achieved by open access. Despite this one case of bleeding, in whom we did not repeat thrombolysis, no bleeding occurred during US-accelerated CDT.

However, four patients developed early recurrent thrombosis after initial successful thrombolysis. In three patients, underlying stenoses were identified which we considered responsible for the recurrent thrombosis. In the case in which the common iliac vein stenosis was only treated by angioplasty resulting in early reocclusion, a stent should have been inserted immediately to optimise adequate flow in the iliac vein. The 17-year-old girl with common iliac vein stenosis should have been treated immediately by dilatation and stenting after successful thrombolysis. In the third case, the same mistake was made, but, luckily, this was corrected by repeat thrombolysis, stenting and insertion of an arteriovenous fistula.

These three cases highlight the need for immediate treatment of all underlying obstructive lesions. After

successful re-canalisation of the venous system, residual venous obstruction should be treated immediately by means of angioplasty and stent insertion to avoid these early reocclusions. Therefore, the centres treating those patients should have the necessary stents immediately at hand to perform these stent placements the moment the underlying cause has been detected, even when thrombolysis has not been completed.

Similar findings have been reported by previous authors such as the series reported in the National Venous Registry by Mewissen et al.[7] This registry data demonstrated that standard CDT with urokinase and additional stent placement leads to complete (100%) clot lysis in 31% and partial (50—99%) clot lysis in 52% of cases. The primary patency rate for all patients in this registry was 65% and 60% at 6 and 12 months, respectively. These patency rates are similar to the 6-month patency rates reported for standard CDT combined with anticoagulation, in two randomised controlled trials by Elsharawy et al.[15] and Enden et al.[16] The degree of lysis was found to be a significant predictor of early and continued patency. In cases of complete clot lysis, 75% of veins remained patent after 1 year, compared with only 32% of veins in cases of insignificant (<50%) lysis. Moreover, subgroup analysis revealed two important observations for iliofemoral DVT: in the subgroup of patients with acute primary iliofemoral DVT, 65% complete clot lysis was noted, and 1-year patency in this complete lysis group was 96%. This suggests that patients with iliofemoral DVT would benefit most from CDT. In addition, Comerota et al.[17,18] have demonstrated that successful CDT in iliofemoral DVT significantly improves quality of life (QoL) compared with failed thrombolysis or anticoagulant therapy alone.

An additional advantage of CDT is the ability to detect and treat underlying lesions (e.g., May—Thurner syndrome) immediately after or during thrombolysis. Balloon dilatation with or without stent placement improves long-term patency,[7,19] and can help prevent DVT or prolong the interval to a recurrent DVT.[4] Mewissen et al. have demonstrated that adjunctive stent placement in the iliac vein significantly improves patency: at 1 year, 74% of limbs treated with stent placement after thrombolysis remained patent, compared with only 53% of limbs without stent placement ($P < 0.001$).[7] Bækgaard et al. more recently confirmed, in a large series of patients ($n = 101$), that additional stenting after CDT in iliofemoral DVT results in excellent long-term patency rates (82% patent veins at 6 years).[19]

Two previous series using US-accelerated CDT have demonstrated considerably increased complete clot lysis rates and fewer complications than standard CDT.[5,6] Whereas only 31%[7] of patients in the National Venous Registry treated with standard CDT exhibited complete clot lysis, 83%[5] versus 85.7%[6] of patients treated with US-accelerated CDT using urokinase had complete clot lysis. The major bleeding rate was 11% and the thrombo-embolic rate 1%[7] with standard CDT, compared with 0%[5] to 3.8% and[6] 0%, respectively, in US-accelerated CDT.[5,6]

Conclusion

US-accelerated CDT using EKOS Endowave® was found to be a feasible technique for managing iliofemoral venous thrombosis resulting in low morbidity and mortality. All underlying obstructive vein lesions should be treated immediately by venoplasty and stenting to prevent early reocclusion. However, randomised controlled trails are needed to evaluate the long-term benefit of endovenous thrombolysis in patients with acute DVT.

Conflicts of Interest

None.

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