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US-accelerated catheter-directed thrombolysis for the treatment of deep venous thrombosis

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PURPOSE
We aimed to evaluate the efficacy and feasibility of ultrasonography (US)-accelerated catheter-directed thrombolysis for the treatment of deep venous thrombosis.

MATERIALS AND METHODS
A total of 26 patients with deep venous thrombosis were prospectively selected for thrombolysis. Overall, 80.8% of the occlusions were in the lower extremities, and 19.2% were in the upper extremities. US-accelerated catheter-directed thrombolysis was performed using a recombinant human tissue plasminogen activator (alteplase), which was delivered using the EKOS EkoSonic® Endovascular System (EKOS Corporation, Bothell, Washington, USA). Postprocedure venography was repeated after the treatment, which included angioplasty and stenting if stenosis was present.

RESULTS
Thrombolysis was successful in 92.3% (24/26) of the patients, with complete clot lysis in 14 patients and partial clot lysis in nine patients. The mean symptom duration was 54.9±51 days (range, 6–183 days), and the mean thrombolysis infusion time was 25.3±5.3 hours (range, 16–39 hours). Pulmonary embolism was not observed; however, there were three cases of bleeding at the catheter insertion site. In three patients, the underlying lesions were successfully treated with balloon angioplasty and stent insertion. Two patients developed early recurrent thrombosis due to residual venous obstruction.

CONCLUSION
US-accelerated thrombolysis was demonstrated to be a safe and efficacious treatment for deep venous thrombosis in this study. The addition of US reduces the total infusion time and increases the incidence of complete lysis with a reduction in bleeding rates. Residual venous obstruction should be treated by angioplasty and stent insertion to prevent early rethrombosis.

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Deep venous thrombosis (DVT) of the lower extremities is a common cardiovascular condition with substantial morbidity and mortality, which occurs in approximately one to two per 1000 persons per year (1).

DVT of the lower and upper extremities has been widely documented as a frequent cause of pulmonary embolism and post-thrombotic syndrome (PTS). The management of DVT has traditionally been based on the long-standing view of the disease as an "acute" condition that includes an initial period of high risk for pulmonary embolism followed by a progressively reduced risk of harm to the patient over time (2). Furthermore, DVT may cause severe short-term morbidity due to phlegmasia cerulea dolens or venous gangrene, which may necessitate amputation of the affected limb. Long-term morbidity is caused by chronic venous hypertension, which leads to PTS (3).

Treatment of DVT has focused on preventing pulmonary embolism, which is a potentially life-threatening complication, rather than on removing or reducing the thrombus. Traditionally, anticoagulation (heparin followed by oral anticoagulation) has been the mainstay for DVT therapy (4, 5). Anticoagulation is currently the standard care for the prevention of pulmonary embolism and recurrent DVT; however, this treatment is ineffective at reducing thrombus burden and consequently does not prevent PTS. Prolonged venous obstruction before complete clot resolution may lead to permanent valvular damage, which is responsible for the post-thrombotic symptoms and long-term morbidity that are associated with DVT (6).

Recent research has demonstrated that patients with PTS have a poorer quality of life than patients of a similar age with diabetes, arthritis or chronic lung disease have, whereas patients with severe PTS report a quality of life that is similar to that of patients with angina, cancer or congestive heart failure (7). PTS ultimately leads to the development of chronic venous leg ulcers, which occur in up to 10% of DVT patients within two years (8) and cause considerable morbidity and a high financial burden (9).

Endovascular catheter-directed thrombolysis (CDT) techniques with pharmacological thrombolytic agents are highly effective at clearing thrombi, which may preserve venous valve function and prevent subsequent venous occlusive disease (10).

Ultrasonography (US)-accelerated CDT has been developed to rapidly and completely resolve thrombi, thus decreasing the potential risk for PTS (11, 12). This technique integrates high-frequency, low-intensity US with standard CDT to accelerate clot dissolution, which reduces treatment time and the incidence of thrombolysis-related complications. US waves increase clot permeability by affecting the fibrin strands in chronic thrombosis, thus facilitating the delivery of therapeutic agents into the clot (13, 14).

The use of CDT to treat DVT may reduce long-term morbidity in DVT patients by restoring the patency of the veins. In this study, we analyzed the efficacy and safety of US-accelerated CDT for the treatment of DVT and investigate the development of PTS.

Materials and methods

Patient population

From September 2009 to May 2012, consecutive patients with clinical and duplex scan diagnoses of DVT were enrolled in this study. The inclusion criterion for thrombolytic therapy was the presence of acute or chronic DVT in the upper or lower extremities for six months or less without any history or diagnostic evidence of previous episodes of DVT. Written informed consent was obtained from each enrolled patient or from the family after the purpose and the risk of the treatment were fully explained. The Institutional Committee of Ethics in Research approved this clinical research project. The patients mainly presented with swelling, pain, and edema of the affected limbs.

Patients who met the inclusion criterion were excluded if any of the following features were present: contraindications to the use of thrombolytic agents, such as a history of major bleeding; recent delivery or major surgery (up to 10 days before the study onset); neurosurgical intervention (up to three months); recent significant trauma; or disease with a known risk of hemorrhagic complications. In addition, patients with isolated infrapopliteal thrombosis, recurrent ipsilateral DVT, pre-existing leg ulcers, a short life expectancy, and contraindications to the use of anticoagulation, contrast media or thrombolytic agents were excluded.

US-accelerated thrombolysis procedure

Venous access was obtained according to the standard practice of each investigator, which typically involved the vein distal to the occlusion (i.e., the basilic or brachial vein in the upper extremity and the posterior tibial or popliteal vein in the lower extremity). Subtherapeutic doses of heparin were administered in most cases through a peripheral catheter or a vascular sheath. The procedures were performed in the angiography suite. Patients were catheterized with a 6 F micro access set under US guidance using a 21 G needle and a 0.46 mm diameter guide wire. Ascending venography was performed. US-accelerated CDT was performed using the EKOS EkoSonic® Endovascular System (EKOS Corporation, Bothell, Washington, USA). A 5.2 F multilumen drug delivery catheter and matching US coaxial core wire were provided by the manufacturer with treatment zone lengths that varied between 6 and 50 cm (Fig. 1). The drug delivery catheter was navigated over a 0.035 inch guidewire to ensure 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 that contained a series of US transducer elements (2.2 MHz, 0.45 W), which were 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 subtherapeutic heparin (1000 U/mL), a continuous infusion of the thrombolytic agent was initiated through the side-holes of the US-accelerated CDT infusion catheter along the treatment zone. A recombinant human tissue plasminogen activator, alteplase (Actilyse®, Boehringer Ingelheim GmbH&Co, Ingelheim, Germany), was administered in a 5 mg bolus followed by an infusion at 0.02 mg/kg/hour for 24 hours. In addition, normal or heparinized saline solution was continuously infused through the central lumen of the catheter at a rate of 35–70 mL/hour to dissipate any amount of heat that was generated by the US energy. US energy was delivered via the core wire with a simultaneous infusion of the thrombolytic drug.

Patients were followed up in the intensive care unit and continuously monitored to detect clinical signs and symptoms of complications, such as pulmonary embolism or hemorrhages. Blood samples were taken every 12 hours to test hematocrit levels, hemoglobin levels, partial thromboplastin time, fibrinogen levels, and platelet counts to adjust the heparin dose and detect blood loss.

After thrombolysis, additional adjunctive procedures were performed if there was an underlying vein stenosis that was greater than 50%. The adjunctive procedures consisted of angioplasty and stent implantation. Postprocedure venography was performed before removing the introducer.

Figure 1. The EKOS EkoSonic® Endovascular System consists of a multi-lumen infusion catheter with a removable coaxial US core and a control unit that simultaneously delivers high-frequency, low-energy (2.2 MHz, 0.45 W) US energy and thrombolytic drugs into the thrombus. US exposure enhances the permeability of the thrombus to the lytic agent. The picture of the catheter is courtesy of the EKOS Corporation, Bothell, Washington, USA.

Warfarin sodium was routinely started before hospital discharge; this treatment was continued for at least six months and the dose was adjusted to maintain an international normalized ratio of 2.0 to 3.0. Adjuvant elastic compression therapy was recommended for more than one year.

Assessment of venous recanalization

Thrombolysis and venous recanalization was determined by comparing pre- and posttreatment venography, and the results were categorized as follows: "complete" recanalization for a 95%–100% restoration of patency, "partial" for 50%–95% and "minimal" for less than 50% due to residual stenosis or an organized thrombus (15, 16). Recanalization was calculated after the completion of treatment, which included US-accelerated CDT and any additional adjunctive procedures. The final score was calculated using the percentage difference between the pre- and posttreatment venographies. The differences in the phlebography values were used to estimate the percentage of thrombolysis, and a 50%–100% removal of the thrombus was considered technically satisfactory. Clinical success was defined as significant resolution of lower extremity pain and swelling (10).

Definitions and follow-up

After hospital discharge, the patients were followed up weekly in the outpatient clinic during the first month and monthly thereafter. At each visit, a patient underwent a clinical evaluation according to a modified Villalta scale (17) and a Doppler US assessment of the affected lower limb. The scope of this procedure was to confirm patency of the deep venous system, the presence of residual thrombi in the treated vein segments, and the presence of venous reflux. The presence of five leg symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and six objective signs (pretibial edema, skin induration, hyperpigmentation, new venous ectasia, redness, and pain during calf compression) was 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: severe PTS was defined as a total score greater than 14 points or a venous ulcer, mild PTS was defined as 5–14 points, and no PTS was defined as less than five points. Valvular reflux was defined as a valve closure time greater than 0.5 s after distal compression and release using an ultrasonic probe in a non-weight-bearing limb when the patient was in the standing position (18). Primary patency was defined as confirmed patency and <50% restenosis as documented by Doppler US (19).

Statistical analysis

A statistical analysis was performed using GraphPad Instat software (version 11.5 for Mac, GraphPad Software Inc., La Jolla, California, USA). All of the values were expressed as the mean ±standard deviation (SD). A comparison of the variables within the groups was conducted using the Wilcoxon test and the nonparametric Spearman rank correlation coefficient test as a post-test. A P value < 0.05 was considered statistically significant.

Table 1. Patients' baseline characteristics

Variable	Value
Age (years), mean±SD (range)	50.6±17.1 (21–74)
Gender (female/male), n	14/12
Reported symptom duration (days), mean (range)	54.9 (6–183)
Affected limb (left/right), n	16/10
Thrombosis location, n (%)	
Upper extremity	5 (19.2)
Lower extremity	21 (80.8)
Symptom duration, n (%)	
Acute (<14 days)	6 (23)
Subacute (15–28 days)	8 (30.8)
Chronic (>28 days)	12 (46.2)
Risk factors, n	
Postpartum	3
Postoperation	5
Trauma	4
Prolonged immobilization	3
Malignancy	2
Idiopathic	9

Results

Patients

Of the 42 eligible patients with an episode of proximal DVT in the upper or lower extremity, 16 patients were excluded because of previous ipsilateral DVT (n=7), recent major surgery (n=4), a poor life expectancy (n=1), contraindications to the use of anticoagulation and contrast media (n=2), or the inability to attend follow-up visits (n=2). The remaining 26 patients were enrolled in this study. The baseline characteristics are reported in Table 1. In lower extremity DVT, the proximal end of the thrombosis reached into the vena cava inferior in three patients, the iliac vein in six patients, and the femoral vein in twelve patients. The mean total alteplase dose was 37±9.2 mg (range, 20–54 mg), and the mean infusion time was 25.3±5.3 hours (range, 16–39 hours).

Assessment of venous recanalization

Overall clot lysis (i.e., the sum of partial and complete thrombolysis) was confirmed through venographic assessment and was achieved in 92.3% of the patient population. Complete clot lysis (>95% restored patency) was achieved in 14 patients (53.8%), and partial clot lysis (50%–95% restored patency) was achieved in an additional 10 patients (38.4%). In two patients, thrombolysis was not successful with minimal clot lysis (<50%), and these patients experienced a chronic thrombus that did not respond to adequate

thrombolysis (133 and 154 days since the onset of symptoms). The initial results of the thrombolysis are summarized in Table 2.

The percentage of thrombolysis was greater than 50% in 24 patients. Significant or complete clinical improvement occurred in 22 of the 26 individuals. Figs. 2 and 3 illustrate the representative cases.

No correlations were observed between the dilution or the dose of the alteplase infusion and the percentage of lysis or clinical improvement. However, a statistically significant correlation was found between the infusion time and the percentage of thrombolysis ($P < 0.0001$) and between the clinical duration of DVT and the percentage of thrombolysis ($P < 0.0001$) (Table 2). In addition, a statistically significant correlation was found between the percentage of thrombus removal and the degree of clinical improvement ($P < 0.01$, Table 3).

Complications

During the treatment period, three patients (11.5%) experienced minor bleeding at the catheter insertion site, which was controlled in all of the cases by simple elevation of the limb and application of a compressive bandage and did not require a transfusion or interruption of the procedure. One patient who experienced bleeding at the catheter insertion site displayed hematuria after 25 hours on alteplase with spontaneous remission after the interruption of lysis. Six patients (23%) complained of slight pain in the affected knees (intramuscular hemorrhage or hemarthrosis was excluded by US and X-ray examination). None of the patients suffered from intracranial hemorrhage, symptomatic pulmonary embolism, death, or other procedure-related complications.

Adjunct procedures

Adjunct procedures, including balloon angioplasty and stent placement, were performed to improve venous flow after thrombolytic treatment. In three cases, underlying iliac vein stenosis was diagnosed and successfully treated with balloon angioplasty and

Table 2. Clinical improvement and initial results of thrombolysis

Patient number	Limb side	Onset of symptoms (days)	Thrombolysis (%)	Clinical improvement	Infusion time (hours)	Alteplase dose (mg)	Venous stenosis or occlusion	Complications
1	L	59	75	++	24	38		
2	L	34	100	+++	16	24		
3	R	10	100	+++	18	20		
4	L	125	71	++	27	41		Hematuria
5	R	47	100	+++	18	27		
6	R	6	95	+++	24	28		
7	L	76	66	+	23	34		
8	L	183	70	++	34	54	CIV	
9	R	18	95	++	28	43		
10	L	24	100	+++	26	38		
11	R	77	95	++	39	45		Hematoma
12	L	113	72	++	30	48		
13	L	11	78	++	28	42		
14	R	12	85	+++	21	26		
15	L	27	83	++	27	40		
16	L	25	100	+++	20	30		
17	R	87	76	+++	22	46		Hematoma
18	R	22	100	+++	24	30		
19	L	133	35	-	30	45	CIV	
20	R	13	95	++	26	39		
21	L	26	95	+++	23	34	CIV	
22	L	154	28	-	30	50		
23	L	24	100	+++	23	35		
24	R	19	95	+++	25	31		
25	L	96	60	+	33	51		
26	L	8	100	+++	19	24		

(-), absent; (+), poor; (++), significant; (+++), complete; CIV, common iliac vein; L, left; R, right.

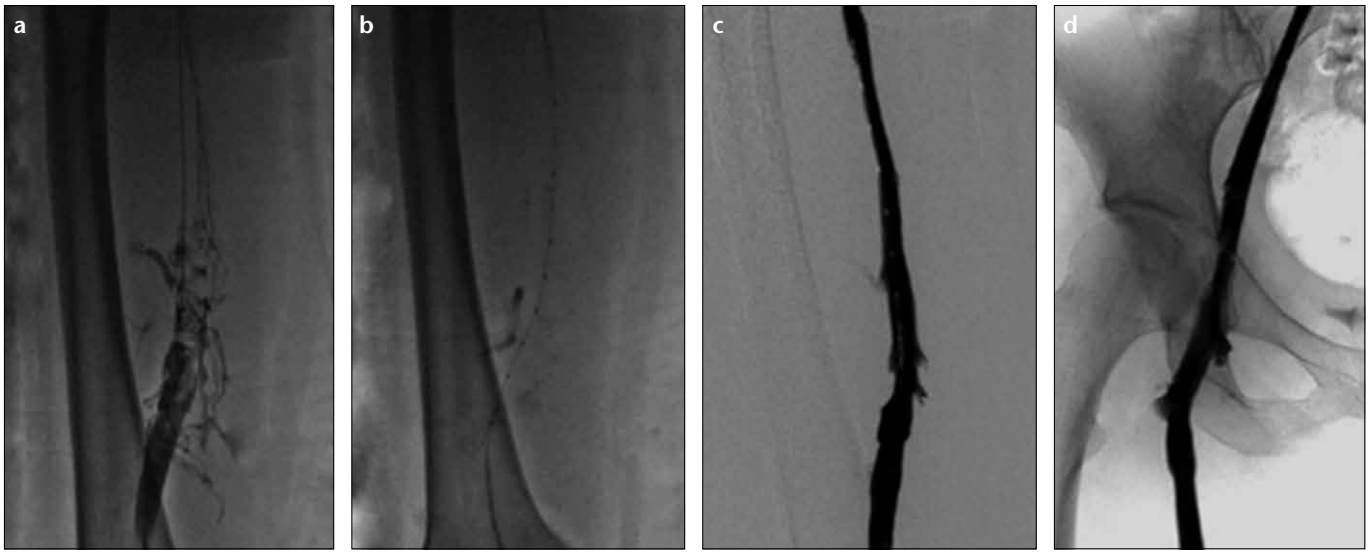

Figure 2. a–d. Images from a 34-year-old female patient who presented with left lower extremity DVT (prone position) **(a)**. The EKOS catheter with a 50-cm treatment length was placed into the thrombus **(b)**. The follow-up angiogram shows the complete resolution of the thrombus after a 23-hour infusion **(c)**. No underlying stenosis was observed **(d)**.

Table 3. Thrombolysis vs. acute clinical improvement

Clinical response	Number of cases	Percentage of thrombus removal (mean [range])
Absent	2	32.5 (28–35)
Poor	2	59 (35–65)
Significant	9	81.9 (65–100)
Complete	13	93.4 (76–100)

Spearman's R=0.622 ($P < 0.01$)

Table 4. Clinical follow-up outcomes (n=26)

Variable	Value
Follow-up duration (months), mean (range)	12.4 (6–22)
Venous patency, n (%)	
Patent	22 (84.7)
Rethrombosis	2 (7.6)
Occlusion	2 (7.6)
Valve function, n (%)	
Normal	21 (80.8)
Reflux	5 (19.2)
Post-thrombotic syndrome, n (%)	
No	23 (88.5)
Mild	3 (11.5)
Severe	0

stent insertion (60/10 mm, 40/10 mm Nitinol® stent, Zilver 518 Vascular self-expandable stent, Cook Medical Corp., Bloomington, Indiana, USA and 60/16 Wall® stent, Boston Scientific, Natick, Massachusetts, USA, respectively) immediately after thrombolysis. Two patients who received stent implantations developed DVT secondary to the compression of the left iliac vein by the right iliac artery (May-Thurner syndrome). Fig. 3 shows the pre- and posttreatment venography and the angioplasty with stent insertion in the case of a 33-year-old female patient with iliocaval vein thrombosis.

Clinical follow-up

The mean follow-up duration was 12.4 months (range, 6–22 months). Overall, 22 out of 24 patients (91.6%) who were treated successfully with US-accelerated CDT remained patent at 12 months according to Doppler US. One patient with a protein-C deficiency achieved complete lysis but experienced restenosis seven months after treatment. In another patient, left-sided common iliac vein stenosis was unmasked after lysis; however, the patient refused to undergo angioplasty and developed early rethrombosis (two months after lysis) before stenting.

Three patients (11.5%) developed mild PTS that mainly manifested as pain, heaviness, and edema of the affected limbs after activity. In addition, mild pruritus was present in four limbs, but none of these limbs had severe PTS. The median total PTS score was two (range, 0–7), and 19 limbs (73%) had a score of less than three. Valvular reflux occurred in five limbs (19.2%) (Table 4).

Discussion

Standard DVT treatment focuses on adequate anticoagulation to prevent pulmonary embolism and thrombus

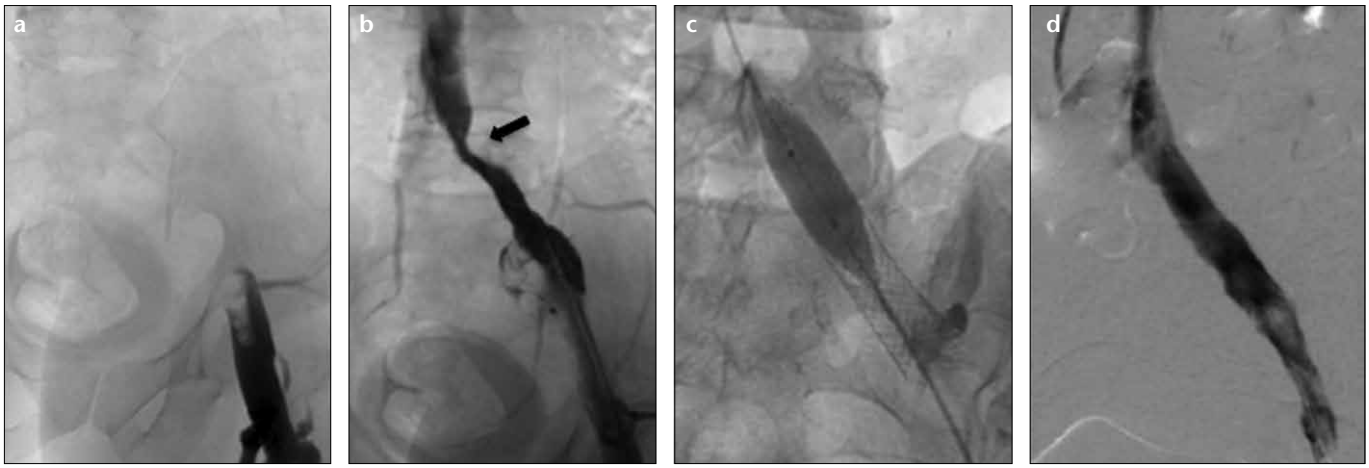

Figure 3. a–d. Venographic images from a 33-year-old female patient who presented with postpartum thrombosis from the iliac vein up to the inferior caval vein **(a)**. After 23 hours of thrombolytic therapy, flow was restored within the common iliac vein; however, there was a focal stenosis in the common iliac vein (*arrow*) **(b)**. The common iliac vein was treated with angioplasty, and a Wall stent (diameter 16 mm, length 60 mm) was deployed to maintain patency in the treated vein **(c)**. The final subtraction venogram shows the complete resolution of iliac vein flow **(d)**.

propagation. However, anticoagulation alone has no direct thrombolytic effect. Current DVT treatments often do not restore venous patency, and venous valves become permanently damaged. In addition, underlying venous stenosis, such as May-Thurner syndrome, which predisposes the patient to recurrent thrombosis, can be left untreated. The prompt and effective removal of acute thrombosis effectively preserves venous valvular function, reduces reflux, and removes venous obstruction. Additionally, this treatment reduces the risk of thrombus recurrence, which is a strong predictor of a poor long-term outcome of DVT and severe PTS (20).

Endovascular thrombolytic methods have evolved considerably in recent years and have prompted discussion and controversy regarding their liberal use. CDT, which involves a local infusion of thrombolytic agents directly into a clot, is an accepted endovascular intervention for the rapid and complete resolution of a thrombus in well-selected patients with DVT.

US-accelerated CDT is a promising technique compared with standard CDT and has several advantages over mechanical techniques, including percutaneous mechanical thrombectomy and embolus fragmentation. Preclinical testing and published clinical case studies about mechanical devices have demonstrated the feasibility and efficacy of these devices in removing acute thrombi in animal models, in vitro models, and humans; however, the risk of vessel wall injury, valvular damage, and pulmonary embolization, which result from vessel wall contact and clot fragmentation, is of concern (21, 22). Because the US-accelerated CDT technique enhances the permeability and penetration of lytics into the thrombus, the thrombus is rapidly and completely dissolved, which prevents the potential complications that are associated with mechanical methods.

The EkoSonic Endovascular System is an US-accelerated thrombolytic system that combines high-frequency, low-intensity US with simultaneous catheter-directed thrombolytics to accelerate clot dissolution rather than fragmentation in the peripheral vasculature. US-enhanced thrombolytic therapy achieves its effect by first disassociating the fibrin mesh to increase the surface area of the thrombus and the fibers that are available to the thrombolytic agent. Simultaneously, acoustic microstreaming, which is caused by the US waves, drives the thrombolytic agent away from the catheter and deep into the loosened clot (23). High-frequency, low-intensity US can be used safely in many medical applications but has no lytic effect. However, the combination of directed US with the local administration of thrombolytic agents accelerates the thrombolytic process (24).

A remarkable feature of the EKOS EkoSonic Endovascular System is that the US energy, which emanates from the transducers, will penetrate venous valves and dissolve thrombi that are located behind the venous valves. Thrombi that are located in this hard-to-reach region are typically inaccessible by other mechanical thrombectomy systems that are used to treat DVT. Because the entire segment of the venous thrombus can be exposed to US energy, this technique reduces the infusion time and the treatment dosage of the thrombolytic agents. CDT methods are currently available for the treatment of DVT as outlined by Pianta and Thomson (25). Motarjeme (26) and Parikh et al. (11) were first to report the use of US-accelerated CDT for the treatment of DVT. They reported significantly higher complete clot lysis rates using US-accelerated CDT compared with standard CDT without an increase in the bleeding or thromboembolic risk. Our study demonstrated considerable patient improvement, which was similar to that observed in previous studies of CDT alone for the treatment of DVT, and involved fewer complications, reduced drug doses, and shorter infusion times. In a National Venous Registry of 287 patients with DVT who were treated with CDT at 63 centers, 83% of patients exhibited a degree of thrombolysis; however, only 31% of patients exhibited complete thrombolysis (10). In comparison, the overall lysis rate in this study was 92.3%, with complete clot lysis in 14 patients (53.8%) and partial clot lysis in ten patients. A single-center pilot study (27) that used tenecteplase in standard thrombolysis for the treatment of DVT reported significant lysis in 83% of cases and a complete lysis rate of 50%. In a retrospective study by Grunwald and Hofmann (28) of 82

patients, 74 of whom were treated for DVT occlusions in the upper and lower extremities, the rates of thrombolysis ranged from 50% to 71% for complete lysis and 96.9% to 100% for overall lysis, and these results are similar to the US-accelerated thrombolysis rates of our study.

A significant percentage of patients have undergone adjunctive procedures, such as angioplasties or venous stenting (29, 30). In our series, three patients had venous stenosis with an indication for angioplasty. Other residual occlusions were observed in sites that are not typically associated with venous stenosis, which later presented with spontaneous recanalization without clinical or duplex evidence of residual stenosis. Segmental occlusions have been observed in patients; however, a significant reduction in thrombotic volume may result in the rapid removal of residual thrombi by the endogenous fibrinolytic system.

Similar findings have been reported by previous authors, such as the series that was reported in the National Venous Registry by Mewissen et al. (10). The primary patency rates at 6 and 12 months for all of the patients in this registry were 65% and 60%, respectively. The six-month patency rate is similar to those reported for standard CDT combined with anticoagulation in two randomized controlled trials by Elsharawy and Elzayat (31) and Enden et al. (32). The degree of thrombolysis was a significant predictor of early and continued patency. In the cases of complete clot lysis, 75% of the veins remained patent after one year compared with only 32% of the veins in the cases of insignificant (<50%) lysis. In our study, US-accelerated CDT was characterized by a lower dose in the infusion and a reduced infusion time, and the venous patency we achieved was similar to that reported by Mewissen.

The mean clinical follow-up time was 12.4 months (range, 6–22 months). Although this time is insufficient to observe late changes that are related to PTS, such as cutaneous hyperpigmentation and phlebopathic ulcers, we believe this time is adequate to detect the early signs of venous insufficiency, such as discomfort, pain, and persistent edema. In our study, three patients (11.5%) suffered from mild PTS, which mainly manifested as pain, heaviness, and edema of the affected limbs after activity. None of the patients in our study had severe PTS according to a modified Villalta scale (Table 4). After one year, valvular reflux occurred in five limbs (19.2%) in our patient series compared with 39 of 106 limbs (37%) in the report by Markel et al. (33). This finding reflects the ability of US-accelerated CDT to effectively preserve valve function and protect against the development of PTS. Of the treated patients, 22 out of 24 (91.6%) indicated good long-term clinical results. This observation supports the use of US-accelerated CDT because this technique results in significantly greater improvement in patients compared with classical anticoagulation therapy for the treatment of extensive DVT.

A statistically significant correlation was found between the percentage of thrombus removal and the degree of clinical improvement ($P < 0.01$, Table 3). In this study, the improvement of symptoms during the acute stage was significantly associated with the success of the thrombolysis and suggested a direct relationship between the volume of the thrombolysis and the degree of clinical improvement. Comerota et al. (34) verified that subjects with DVT who underwent successful thrombolysis had a better quality of life and a lower incidence of PTS symptoms than individuals who were treated only with anticoagulants. This study provides similar evidence of a relationship between the effectiveness of the thrombolytic method and favorable late clinical results, which preserves the quality of life of patients who undergo successful therapy.

In most of the studies on venous lysis of the lower limbs, the selection of patients with acute DVT did not exclude patients who were suffering from previous venous insufficiency. These studies focused their analyses on the immediate results of the thrombolytic treatment. However, the eventual benefits of thrombolysis on the clinical outcomes of the patients were difficult to identify due to the diversity of the patient groups. In our study, we excluded subjects who displayed any evidence of DVT or chronic venous insufficiency before the acute episode. Therefore, we concluded that the presence of residual thrombosis and/or late valvular reflux in several patients was directly correlated with the DVT episode that was analyzed.

This study was a prospective investigation; however, an initial control group with conventional anticoagulation therapy was not created due to the restrictive criteria for patient selection, which resulted in a small number of cases. An appropriate control group would need to be selected from a randomization of patients with the same clinical characteristics, which would have doubled the number of cases required for the study, thus making the study not feasible for a single-center investigation. Alternative nonrandomized control groups of patients who met the exclusion criteria would most likely introduce differences in the incidence and the distribution of factors, such as age, venous insufficiency, and other morbidities, which would result in bias. Furthermore, the follow-up of thrombus removal was performed only with Doppler US imaging, which is the most commonly used method in clinical practice; however, a limitation of this technique is the ineffective or inadequate evaluation of thrombi in the calf region and the iliac veins. These factors are the limitations of the study.

Studies have confirmed that early clot removal can preserve valve function and prevent the long-term morbidity that is associated with DVT. Multiple approaches have been proposed; however, the focus has shifted towards endovascular interventions for DVT. To date, the results of using endovascular interventions for DVT are encouraging and far exceed those that were obtained using anticoagulation alone in the appropriate patient population. US-accelerated CDT is as effective as other mechanical thrombectomy methods, which eliminate the cause of long-term morbidity, including DVT recurrence, rather than preventing thrombus propagation, clinical deterioration, or relapse.

In conclusion, US-accelerated CDT is an interventional procedure that was developed to resolve existing thrombi more completely and more rapidly than traditional endovascular techniques. Moreover, the high degree of complete and partial lysis together with a reduced thrombolytic dosage, shorter infusion times, and a lower rate of bleeding suggest that US-accelerated CDT plays a significant role in the catheter-directed treatment of DVT. Therefore, US-accelerated CDT

represents an attractive therapeutic adjunct in the management of DVT in well-defined patient subgroups.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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