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Original Article / Özgün Makale

Accelerated catheter-directed thrombolytic treatment in deep venous thrombosis: mid-term results

Derin ven trombozunda kateter-aracılı mikrodalga ultrason ile hızlandırılmış trombolitik tedavi: Orta dönem sonuçlar

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ABSTRACT

Background: This study aims to retrospectively analyze the early and mid-term results of ultrasound accelerated catheter-directed thrombolytic treatment (EKOS) performed in our clinic in patients with iliofemoral deep venous thrombosis (DVT).

Methods: In our clinic, EKOS was performed in 16 patients (12 males, 4 females; mean age 50.2±18.2 years; range 20 to 86 years). Deep venous thrombosis was present on the left lower extremity in nine and right lower extremity in seven patients. Mean duration of treatment from the onset of symptoms was 8.2±5.2 days. Additional to standard EKOS, six patients were administered additional thrombolytic via an angiocath placed in dorsal vein of ipsilateral foot in 1/3 dosage. Patients' fibrinogen levels were monitored periodically and thrombolytic treatment was stopped under critical levels with continuation of heparin infusion. Mean duration of thrombolytic infusion was 18.4±9.8 hours (range, 6-48 hours) and mean dose of thrombolytic was 38.2±18.1 mg (range, 13-90 mg).

Results: Complete patency was obtained in seven patients (43.8%). One patient (6.3%) developed post-procedural retroperitoneal hematoma. No mortality occurred during follow-up. Mean and total durations of follow-up were 9.3±8.3 months (range, 0.9-24.3 months) and 148.7 patient/months, respectively. In the final controls, 10 patients (62.5%) were asymptomatic or mildly symptomatic, and two patients (12.5%) had post-thrombotic syndrome. Recurrence of DVT was observed in three patients (18.8%). Recurrence-free average and total durations of follow-up were 7.6±7.3 months and 122.0 patient/months, respectively. No patients had pulmonary emboli during follow-up.

Conclusion: Incidence of post-thrombotic syndrome after DVT with EKOS treatment was lower than the reported 25%-50% incidence in the literature compared to only anticoagulant usage. However, rate of asymptomatic or mildly symptomatic patients was not as high as expected. Larger scale studies and comparisons with other pharmacomechanical treatments are required to evaluate treatment efficiency.

Keywords: Deep venous thrombosis; thrombolytic treatment; ultrasound accelerated catheter-directed thrombolytic treatment.

ÖZ

Amaç: Bu çalışmada kliniğimizde iliofemoral derin ven trombozu (DVT) olan hastalarda uygulanan kateter-aracılı mikrodalga ultrason ile hızlandırılmış trombolitik tedavinin (EKOS) erken ve orta dönem sonuçları retrospektif olarak analiz edildi.

Çalışma planı: Kliniğimizde 16 hastaya (12 erkek, 4 kadın; ort. yaş 50.2±18.2 yıl; dağılım 20-86 yıl) EKOS uygulandı. Dokuz hastada sol ve yedi hastada sağ alt ekstremitede DVT vardı. Semptomların başlangıcından itibaren ortalama tedavi süresi 8.2±5.2 gün idi. Standart EKOS'a ek olarak altı hastaya aynı taraf ayak dorsal venine yerleştirilen bir anjiyoket içerisinden 1/3 dozajında ek trombolitik verildi. Hastaların fibrinojen seviyeleri periyodik olarak takip edildi ve kritik seviyenin altına düşüldüğünde trombolitik kesilerek heparin infüzyonu ile devam edildi. Ortalama trombolitik infüzyonu süresi 18.4±9.8 saat (dağılım, 6-48 saat) ve ortalama trombolitik dozu 38.2±18.1 mg (dağılım, 13-90 mg) idi.

Bulgular: Yedi hastada (%43.8) tam açıklık sağlandı. Bir hastada (%6.3) işlem sonrası retroperitoneal hematom gelişti. Takip sırasında mortalite olmadı. Ortalama ve toplam takip süreleri sırasıyla 9.3±8.3 ay (dağılım, 0.9-24.3 ay) ve 148.7 hasta/ay idi. Son kontrollerde 10 hasta (%62.5) asemptomatik veya hafif semptomatik idi ve iki hastada (%12.5) posttrombotik sendrom vardı. Üç hastada (%18.8) DVT nüksü görüldü. Nükssüz ortalama ve toplam takip süreleri sırasıyla 7.6±7.3 ay ve 122.0 hasta/ay oldu. Takip süresince hiçbir hastada pulmoner emboli yoktu.

Sonuç: Kateter-aracılı mikrodalga ultrason ile hızlandırılmış trombolitik tedavisi ile DVT sonrası posttrombotik sendrom insidansı sadece antikoagülan kullanımına göre literatürde belirtilen %25-%50 insidansından daha düşüktü. Buna rağmen, asemptomatik veya hafif semptomatik hastaların oranı beklendiği kadar yüksek değildi. Tedavi etkinliğinin değerlendirilmesi için daha büyük ölçekli çalışmalar ve diğer farmakomekanik tedaviler ile yapılacak karşılaştırmalar gereklidir.

Anahtar sözcükler: Derin ven trombozu; trombolitik tedavi; kateter-aracılı mikrodalga ultrason ile hızlandırılmış trombolitik tedavi.

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Lower extremity deep venous thrombosis (DVT) is a frequent clinical picture that features significant mortality and morbidity and has reported incidence rates of between 1 and 2% in the general population.[1] The standard therapy for acute DVT is low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKA) together with compression stockings,[2] with the net benefit of this therapy being a decrease in mortality via the prevention of pulmonary embolisms (PEs).

In spite of this therapy, because of post-thrombotic syndrome (PTS), the morbidity rates for this condition range from 25-50%,[3,4] and they climb to more than 50% after two years.[5] The main reason for this is believed to be that oral anticoagulation does not favor thrombolysis but rather a decrease in thrombus propagation. Dumantepe et al.[6] reported that LMWH was more effective in terms of thrombus regression and that it was not inferior to oral VKA in their prospective analysis in which the VKA group had an 8.3% rate of recurrence while the LMWH group had none. The venous reflux rate in their study was also significantly lower in the LMWH group (17.9% vs. 32.2%), and PTS was observed in 15.7% of the LMWH group but more than 40% of the VKA group, which was statistically significant. Similar advantages of LMWH over VKA were also observed by Haliloğlu et al.[7] who reported lower venous reflux rates and higher recanalization rates with heparin usage.

Systemic thrombolysis has previously been investigated as a means to achieve lysis of the thrombus, but it was not successful in terms of thrombus clearance. Moreover, it had very high hemorrhagic complications.[5] In addition, the initial reports of ultrasound-accelerated catheter-directed thrombolysis (UACDT) that have been published since 2007 by various authors[8-10] have reported higher complete clot lysis rates without significant morbidity rates.[11] Furthermore, Dumantepe et al.[12] used high frequency, low intensity ultrasound (US) integrated with catheter-directed thrombolytic (CDT) to rapidly dissolve the thrombus and the subsequent related complications of DVT. Moreover, the most recent guidelines have recommended CDT therapy in order to avoid the development of PTS.[2,13] Herein, we report the early and mid-term follow-up results associated with the use of UACDT at our institution.

PATIENTS AND METHODS

Sixteen consecutive DVT patients (12 males, 4 females; mean age 50.2±18.2 years; range 20 to 86 years) who had completed their post-discharge follow-up were treated with UACDT (Ekosonic® Endovascular System, EKOS Corporation, Bothell, WA, USA) from September 2012 to May 2014. Only those with acute DVT symptoms of 14 days or less (with the exception of one patient) and a low risk of bleeding were treated with this type of thrombolysis. Patients with the following features were excluded from the study: the presence of any contraindication to the use of thrombolytic agents (e.g., a major history of bleeding, recent delivery of a baby, or major surgery within three months of beginning UACDT), a neurosurgical intervention that occurred within three months of beginning UACDT, recent significant trauma, previously known hemorrhagic diathesis, isolated thrombosis of the calf veins, recurrent DVT in an ipsilateral limb, pre-existing PTS, a short life expectancy, or contraindications to the use of anticoagulation or contrast media. Furthermore, those patients who were lost to follow-up were not included in the analysis. This retrospective study was approved by the institutional ethics committee.

When possible, a 16-gauge (16G) peripheral venous cannula was inserted into the ipsilateral dorsal vein of the foot before the procedure, which was performed in the operating theatre with the portable Ziehm 8000 featuring C-arm technology (Ziehm Imaging GmbH, Nuremberg, Germany). Venous access was obtained via the popliteal vein in all of the cases. Next, the patients were anticoagulated with 5000 IU unfractionated heparin through the vascular sheath and catheterized via US guidance using a 21G needle and a 0.46 mm guidewire. Ascending venography was then performed with a hand-held syringe. The endovascular device had a 5.2 French (5.2 Fr) drug delivery catheter with multiple lumens, and the treatment zone lengths of the catheters varied between 30 and 50 cm. This catheter was navigated over a 0.038 inch guidewire to ensure that the treatment zone traversed the entire clot, and the tip then exited the thrombus. The guidewires were supported with a 5 Fr vertebral catheter when necessary.

After the outer catheter was inserted, the guidewire was exchanged for a corresponding US core wire lined with US transducer elements (2.2 MHz, 0.45 W). Afterwards, the drug lumens of the catheters were flushed with unfractionated heparin (1000 U/mL), and the patients were transferred to the cardiovascular intensive care unit (ICU) for continuous infusion of the thrombolytic agent via the UACDT catheter. Alteplase (Actilyse®, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany) was then administered as an infusion at 0.05 mg/kg/hour, and the doses were

titrated in saline solutions so that the infusion rates were kept at 64 mL/hour.

In addition to conventional treatment with the UACDT device, six patients also received additional one-third thrombolytic doses via the dorsal vein of the ipsilateral foot along with the external compression of the saphenous vein at ankle level. Moreover, each patient received a heparinized saline solution (25,000 IU/1,000 mL) infusion through the central lumen of the catheter at a rate of 35-70 mL/hour to dissipate any amount of heat that had been generated by the US energy.

The thrombolytic infusions were administered in the cardiovascular ICU, and the patients were continuously monitored for complications, such as PE or hemorrhaging. Blood samples were taken every six hours to test the hematocrit (Hct) and fibrinogen levels, partial thromboplastin time (PTT), and platelet counts to detect any bleeding and adjust the heparin dosage if needed. In addition, the monitorization and adjustment of the thrombolytic infusion was done by checking the periodic fibrinogen levels every six hours. The treatment was stopped when the fibrinogen levels decreased below the threshold levels (<100 mg/dL), and it was not continued unless the levels increased in the next two measurements. These six patients received a heparin infusion during the cessation periods.

After the thrombolysis, the procedural success was evaluated using venography before removing the introducer. Warfarin sodium was routinely started after the removal of introducer sheath and was continued according to the guidelines published in 2012.[2] Additionally, adjuvant elastic compression therapy was recommended for at least the next two years.

The success of the procedures was determined by comparing the pre- and post-procedural venography results. The outcomes had been previously defined as "complete" (>95% patency), "partial" (50-95% patency), and "minimal" (<50% patency) recanalization,[12,14,15] and Mewissen et al.[16] defined clinical success as a significant resolution of lower extremity pain and swelling.

The patient follow-ups were carried out in the outpatient clinic on a weekly basis for the first month after being discharged from the hospital, then monthly for three months, and every three months for the subsequent year. The clinical picture was evaluated at each control using a modified Villalta scale as described by Kahn et al.[17] Furthermore, Doppler US was used to assess the affected lower limb at the first, third, sixth, and 12th months and yearly thereafter. Plus, it was utilized to evaluate the patency of the deep venous system and venous reflux associated with residual thrombi. The Villalta scale assesses the presence of leg symptoms (pain, cramping, heaviness, itching, and paresthesia) and the physical examination findings (pretibial edema, induration, hyperpigmentation, new venous ectasia, redness, and pain with calf compression), and each symptom and finding is assigned a score of 0 (none), 1 (mild), 2 (moderate), or 3 (severe). The clinical pictures of the patients in our study were evaluated according to the following scale: a total score of <14 points or the appearance of a venous ulcer indicated severe PTS while a score of between 5 and 14 indicated mild PTS. A score of <5 meant that no PTS was present.[17] Primary patency was diagnosed when Doppler US confirmed the patency and revealed <50% restenosis.[12]

Statistical analysis

Statistical analyses were performed using the SPSS version 15.0 for Windows software program (SPSS Inc., Chicago, IL, USA). All of the data was presented as either frequencies and percentages or mean ± standard deviation (SD) accordingly, and the comparisons of discrete data were performed using a chi-square or Fisher's exact tests where appropriate. The comparisons of continuous data were made using the Mann-Whitney U test, and a p value of <0.05 was considered to be significant.

RESULTS

The baseline characteristics of the patients are outlined in Table 1, which shows that three patients had a history of venous thromboembolism (VTE). In addition, they had DVT in their contralateral limbs and one also previously suffered from PE.

The procedural characteristics and outcome results are given in Table 2. One striking feature is that out of the 16 patients analyzed, two had infusions for six and 12 hours respectively due to decreased fibrinogen levels.

Complete patency was obtained in seven of the patients (43.8%) at the end of the procedure, but one (6.3%) experienced periprocedural morbidity (retroperitoneal hematoma). No mortality occurred during the follow-up period. In the final controls, 14 (87.5%) had mild symptoms or no symptoms at all, and two (12.5%) had PTS. Furthermore, 14 (87.5%) had Villalta scores of <5, and two had mild PTS

Table 1. Baseline characteristics of the patients

Variable	n	%	Mean±SD	Range
Age (years)			50.2±18.2	20-86
Gender				
Male	12	75		
Affected limb				
Left	9	56.3		
Right	7	43.7		
Symptom duration in days			8.0±5.1	3-21
>14 days	3	18.8		
Presence of a predisposing factor	6	37.5		
Prolonged immobilization (>3 days)	3			
Surgery	1			
Malignancy	1			
Thrombophlebitis	1			
History of venous thromboembolism in a contralateral limb	3	18.8		

SD: Standard deviation.

(Table 2). Venous insufficiency was also detected in three patients (18.8%) during follow-up. Two of these had continuous regurgitation in the common and superficial femoral veins, and the other had a reversed flow that lasted one second in the common femoral vein. However, no patients had PE during follow-up.

The average and total durations of the follow-up period were 9.3±8.3 (range 0.9-24.3) months and 148.7 patient-months, respectively. Recurrence of DVT was seen in three of the patients (18.8%), with two of these cases occurring within the first six months of the thrombolytic therapy while the patients were still on warfarin. They both had partial patency after the UACDT. The other patient had a recurrence 1.1 years after the procedure following the cessation of warfarin therapy, but she had complete patency after the procedure. The average and total durations of recurrence-free follow-ups were 7.6±7.3 (range 0.2-24.3) months and 122.0 patient-months, respectively.

Post-discharge venography was performed on two patients (Figures 1 and 2). The first was a 48-year-old male (Figure 1) who received UACDT seven days after the onset of symptoms. A 40 cm therapeutic catheter (EKOS Corporation, Bothell, WA, USA) was then inserted, and a total of 90 mg of alteplase was administered over a 48-hour period without dorsal foot infusion. His control venography revealed partial patency, and he was taking warfarin and using compression stockings when we calculated that he had a final Villalta score of 2 at his final follow-up. The second patient was a 20-year-old male who received UACDT 21 days after the onset of symptoms (Figure 2). A 30 cm catheter was inserted, and he received 60 mg of alteplase over the next 36 hours without foot vein infusion. He also had partial patency in the control venography. At the final control, he was still on warfarin and was using compression stockings. His Villalta score was 2 at the final follow-up appointment.

Table 2. Procedural characteristics and outcome results

Variable	n	%	Mean±SD	Range
Length of therapeutic segment				
30 cm	2	12.5		
40 cm	12	75		
50 cm	2	12.5		
Alteplase usage				
Total dose in mg			38.2±18.1	13-90
Duration of infusion in hours			18.4±9.8	6-48
Infusion via dorsal vein of the foot	6	37.5		

SD: Standard deviation.

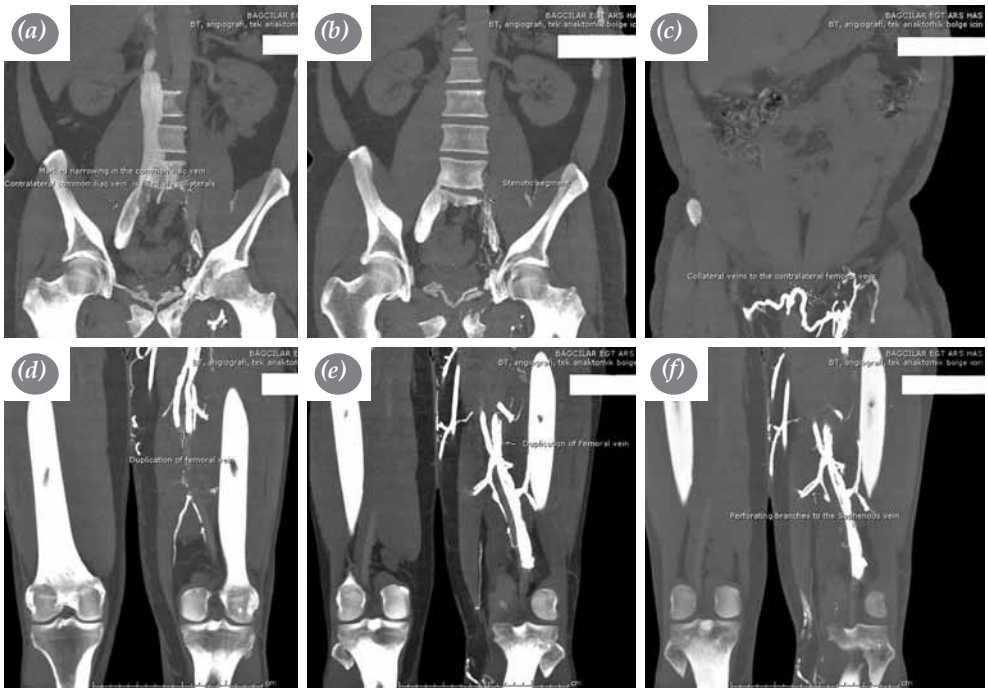

Figure 1. Control computed tomographic venography of a patient three months after the procedure.

We also evaluated the use of the dorsal vein as an additional route for alteplase infusion in terms of outcomes (Table 4), and the only statistically significant difference was the lower duration of thrombolytic infusion, which was due to the decreased fibrinogen levels. Although no statistical significance was noted, none of these patients suffered from venous insufficiency.

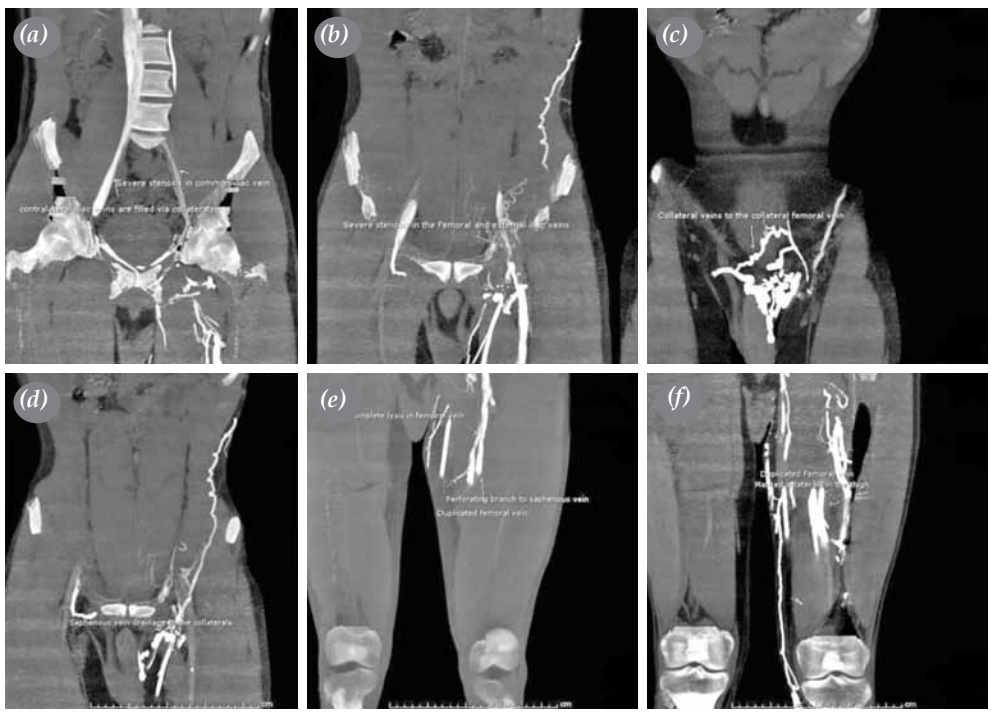

Figure 2. Control computed tomographic venography of a patient eight months after the procedure.

Table 3. Post-discharge results

Variable	n	%	Mean±SD	Range
Villalta score			2.8±2.4	0-10
Patients with ≥5 Villalta score	2	12.5		
Venous insufficiency	3	18.8		
Anticoagulant-related complication	None			
Deep venous thrombosis recurrence	3	18.8		
Pulmonary emboli	None			

SD: Standard deviation.

DISCUSSION

There are several options for thrombus removal in DVT treatment. The most recent guidelines of the Society of Vascular Surgery (SVS) and the American Venous Forum (AVM) recommended the use of early thrombus removal for patients with this condition for <14 days as well as those with iliofemoral thrombosis and a low risk of bleeding. It was also recommended for patients who were ambulatory and in good condition and those with an acceptable life expectancy.[13] In addition, they preferred pharmacomechanical modalities over CDT alone[13] when there were available resources. In their retrospective analysis of pharmacomechanical treatment for DVT Rao et al.[18] reported that 16 out of 43 patients received thrombolytic therapy and that the EKOS therapeutic system had been utilized on eight of the 16 patients. Furthermore, in their study, CDT was used selectively only for those with a thrombosed intravenous catheter.

One of the most serious complications after DVT is PTS. The average Villalta score of our patient cohort was 2.8 (Table 2), but the scores for two of our patients (12.5%) were >5. Results similar to ours have been reported with CDT in the literature.[19,20] Comerota et al.[19] showed that high Villalta scores were correlated with residual thrombi. Additionally, Özçınar and Gökalp[21] reported successful lysis in approximately 70% of their small patient group, and in the early follow-up period, no recurrences were detected. They also found that 29.4% of the patients experienced functional venous obstruction and that more than 50% had venous insufficiency. However, the status of PTS was not addressed in their analysis. Dumantepe et al.[12] reported that 11.3% of their patients had PTS after more than 12 months of follow-up, and this occurred in spite of having higher patency rates after the procedure than in our series. In our patient cohort, there was chronic DVT in three patients (Table 3) during follow-up, but our venous insufficiency and PTS rates (Table 3) were comparable to other studies in the literature.[12] The relatively better clinical status of our patients compared with the low patency rates was probably related to the development of collaterals

Table 4. Comparison of patients who had alteplase infusion via the dorsal foot veins

Variable	Group D			Group N			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Therapeutic length of EKOS catheter							0.350
30 cm	1	16.7		1	10.0		
40 cm	5	83.3		7	70.0		
50 cm	–	–		2	20.0		
Alteplase usage							
Total dose, mg			27.5±11.7			39.0±20.2	0.187
Duration of infusion, hours			13.2±4.1			21.2±11.3	0.046
Complete patency in control venography	2	33.3		5	50.0		0.633
Complications	1	16.7		0	0		0.375
Villalta score			2.5±2.2			3.0±2.7	0.147
Post-thrombotic syndrome	1	16.7		1	10.0		1.000
Venous insufficiency	0	0		3	30.0		0.250
Deep vein thrombosis recurrence	1	16.7		2	20.0		1.000
Pulmonary emboli	None						

SD: Standard deviation; EKOS: Ultrasound accelerated thrombolysis; Group D received alteplase infusion via the dorsal vein of the ipsilateral foot while group N did not receive additional alteplase infusion.

(Figures 1c, 2c, d) and the medical therapy with compression stockings. Although the presence of residual thrombi and any DVT has been associated with more severe clinical pictures,[19,20] the appearance of collaterals and the effects of the prescribed medical treatment should not be overlooked.

The timing of CDT was a matter of debate in the Adjunctive Catheter-Directed Thrombolysis (ATTRACT) and the Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis (CaVenT) trials[22,23] which had cut-off limits of 14 and 21 days, respectively. The most recent guidelines, on the other hand, accepted 14 days as the cut-off for CDT in DVT treatment.[2,13] Dumantepe et al.[24] reported successful results in DVT patients who were admitted for an average duration of more than 90 days. Of their 12 patients, lysis six had complete while five had partial lysis with an average duration of 26 hours. In our series, three patients had DVT for more than 14 days. Two of them received 16 mg of alteplase over a 16-hour period, and the other was given 60 mg over the next 36 hours. All three of these patients had partial lysis. In addition, one of these patients who received the 16-hour infusion and had a 15-day history of DVT had a Villalta score of 10, but the other two were doing well with Villalta scores of 2 at the final follow-up.

One of the most critical complications associated with thrombolytic therapy is bleeding. The accepted limit of bleeding for CDT procedures is 15%,[25] but in order to decrease the duration of the therapy, we preferred higher unit doses than had previously been reported in the literature.[12]

Another important aspect of our experience was the use of dorsal foot veins for additional thrombolytic doses. We used this approach in six patients with two purposes in mind. The first was to give high doses over a short period of time, and the second was to provide lysis in the calf segments and enhance continuous flow in the sequential venous segments so as to augment venous function and the clinical picture according to the open vein hypothesis.[3,26] Although the number of patients in our study was limited, there was a lower duration of infusion and better preservation of venous function even though there were lower levels of complete patency in our patients (Table 4). The high-volume infusion through the EKOS catheter was also used for this purpose.[26]

In order to detect stenosis during follow-up, computed tomographic venography (CTV) was performed on two of our patients (Figures 1 and 2). Barutça et al.[27] reported that evaluation via Doppler US was very effective in veins in the extremities, but that it was inferior to CTV in the pelvic veins. Because stenosis was detected in our two patients, they remain in medical follow-up, and at the present time, their clinical condition has significantly improved.

The main drawbacks of this study were its retrospective design and the lack of a control group, which could have led to false high complication rates. However, as a treatment modality launched in the last few years, we believe that our institutional results associated with the use of UACDT are beneficial to the cardiovascular society. In addition, the aim of this study was to evaluate the outcomes of this procedure as it relates to our experience, which we believe we accomplished. Some may argue that randomization based on hospital records is too cumbersome, and others might object to the low patency rates after the UACDT in our study. However, there were several explanations for the lower than expected rates. First, some patients did not receive proper doses of thrombolytic therapy because of the marked attenuations in the fibrinogen levels, but the doses we gave were needed to avoid any bleeding complications. Another reason for the lower rates was related to the patients' anatomy, especially in one of the patients who was admitted more than 14 days after the onset of symptoms because he had a duplicated superficial femoral vein that led to the incomplete removal of the thrombus.

Conclusion

The use of UACDT in DVT treatment benefits the patient, especially when follow-up parameters are taken into consideration. Although our patency rates were lower than expected, the patients showed significant improvement and had low complication rates. Although not conclusive, it is possible that the use of dorsal foot vein infusions may augment the follow-up results, but further studies are needed to confirm this hypothesis.

Declaration of conflicting interests

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