



## ARAŞTIRMA / RESEARCH

# Ultrasound accelerated catheter directed thrombolysis for treatment of acute iliofemoral deep venous thrombosis without popliteal vein thrombosis: early and midterm results

Popliteal ven tutulumu olmayan akut iliofemoral ven trombozunun ultrasonla hızlandırılmış kateter aracılı trombolitik tedavisi: erken ve orta dönem sonuçlar

Emre Kubat<sup>1</sup>, Celal Selçuk Ünal<sup>2</sup>, Aydın Keskin<sup>2</sup>, Erdem Çetin<sup>2</sup>

<sup>1</sup>Gülhane Training and Research Hospital, Department of Cardiovascular Surgery, Ankara, Turkey

<sup>2</sup>Karabük Training and Research Hospital, Department of Cardiovascular Surgery, Karabük, Turkey

*Cukurova Medical Journal 2019;44(2):347-353*

### Abstract

**Purpose:** The aim of this study was to assess early and midterm results of the patients undergoing ultrasound-accelerated catheter-directed thrombolysis for the treatment of acute iliofemoral deep venous thrombosis without popliteal vein thrombosis.

**Materials and Methods:** A total of 18 patients (11 males, 7 females; mean age: 51.89±16.29 years; range, 16 to 72 years) who were diagnosed with acute iliofemoral deep vein thrombosis between November 2014 and December 2015 were included in this retrospective cross-sectional study.

**Results:** Complete thrombolysis was successful in 88.9% (n=16) and in % 11.1 (n=2) patients with partial clot lysis. No pulmonary embolism was seen, while bleeding at the catheter-insertion site was observed in one patient. In another patient, underlying lesions were successfully treated with balloon angioplasty. The mean follow-up was 31.56±3.35 (range, 25 to 37 months). Duplex ultrasound was performed at one month, six months, one year, and two years following intervention and the iliac vein patency rate was found to be 100%, while superficial femoral vein insufficiency was in 5.6% (n=1), 11.1% (n=2), 16.2% (n=3), and 16.2% (n=3), respectively.

**Conclusion:** Based on our findings, ultrasound-accelerated catheter-directed thrombolysis is a safe and effective method for carefully selected patients with acute iliofemoral deep vein thrombosis without popliteal vein thrombosis.

**Keywords:** Catheter-directed thrombolysis, deep vein thrombosis, ultrasound

### Öz

**Amaç:** Bu çalışmanın amacı popliteal veni açık olan ilio-femoral derin trombozu nedeniyle ultrason ile hızlandırılmış kateter aracılı tromboliz tedavisi yapılan hastaların erken ve orta dönem sonuçlarını değerlendirmektir.

**Gereç ve Yöntem:** Kasım 2014-Aralık 2015 tarihleri arasında akut iliofemoral derin ven trombozu nedeniyle ultrason ile hızlandırılmış kateter aracılı tromboliz tedavisi uygulanan 18 hasta (11 erkek, 7 bayan; ortalama yaş 51,89±16,29 yıl) retrospektif kesitsel olarak planlanan çalışmaya dahil edilmiştir.

**Bulgular:** Hastaların % 88,9 unda (16/18) komplet tromboliz, 2 hastada parsiyel tromboliz başarıyla sağlanmıştır. Pulmoner embolizm gözlenmedi. Bir hastada kateter yerinde kanama gözlemlendi. Parsiyel lizis olan bir hastada altta yatan lezyon balon anjioplasti ile başarılı olarak tedavi edilmiştir. Ortalama takip süresi 31,56±3,35 aydır. Dopler ultrasonografi kontrolleri girişim sonrası 1 ve 6. ay ile 1 ve 2. yılda yapılarak raporlanmıştır. İliak ven açıklık oranı % 100 saptandı. Fakat sırasıyla 5,6% (1 hasta), 11,1% (2 hasta), 16,2% (3 hasta), 16,2% (3 hasta) yüzeysel femoral vende yetmezlik saptandı.

**Sonuç:** Çalışmamızın sonuçlarına göre, popliteal veni patent olup ilio-femoral derin ven trombozu olan dikkatli seçilmiş hastalarda ultrason ile hızlandırılmış kateter aracılı tromboliz tedavisi güvenli ve efektif bir metottür.

**Anahtar kelimeler:** Kateter aracılı tromboliz, derin ven trombozu, ultrason

Yazışma Adresi/Address for Correspondence: Dr. Emre Kubat, Health Sciences University Gülhane Training and Research Hospital, Department of Cardiovascular Surgery, Ankara, Turkey. E-mail: ekubat@gmail.com  
Geliş tarihi/Received: 16.09.2018 Kabul tarihi/Accepted: 29.11.2018 Çevrimiçi yayın/Published online: 21.02.2019

## INTRODUCTION

Post-thrombotic syndrome (PTS), which is the chronic complication of deep venous thrombosis (DVT), is associated with deep venous insufficiency symptoms. The main early goal of treatment for DVT is to prevent clot propagation and pulmonary embolism and to prevent chronic deep venous insufficiency in the long-term. Compared to lower leg distal DVT, iliofemoral DVT is associated with 25% higher possibility of developing PTS<sup>1</sup>. Standard acute DVT treatment consist of anticoagulation, compression therapy, and mobilization<sup>2</sup>. However, none of these treatments can remove thrombus actively<sup>3</sup>. It has been suggested that persistence of thrombus in the venous system may cause PTS<sup>3</sup>. Despite adequate long-term anticoagulation therapy, the five-year PTS incidence has been reported as 28%<sup>4</sup>. It is considered that early clot lysis may preserve normal venous valve function and decrease the risk of developing PTS<sup>5</sup>.

Catheter-directed thrombolysis (CDT) has been suggested for early clot resolution to protect the valve function and venous vessels competence<sup>2</sup>. It has been also shown that ultrasound-accelerated catheter-directed thrombolysis (UACDT) is a safe and effective method with minimally invasive endovascular strategy for removing thrombus in acute DVT episodes<sup>6,7</sup>.

In the present study, we aimed to evaluate early and midterm results of the patients who underwent UACDT for the treatment of acute iliofemoral DVT without popliteal vein thrombosis.

## MATERIALS AND METHODS

A total of 18 patients (11 males, 7 females; mean age:  $51.89 \pm 16.29$  years; range, 16 to 72 years) who underwent UACDT at the Cardiovascular Surgery Clinic of Karabük Training and Research Hospital between November 2014 and December 2015 were included in retrospective cross-sectional study. Patients' data were collected prospectively for the demographics, indications for treatment, peri-procedural complications, clinical outcomes, and follow-up with Duplex ultrasound (US) imaging findings were retrospectively analyzed. A written informed consent was obtained from each patient. The study protocol was approved by the Karabük University Ethics Committee (28.02.2018 with

Decision No: 3/5). The study was conducted in accordance with the principles of the Declaration of Helsinki.

## Patient selection

Patients, for the first time, presenting with symptomatic occlusive proximal acute DVT (<14 days since the symptom onset) of the iliac vein (with or without common femoral, superficial femoral veins, and without popliteal vein) were selected for the treatment. The diagnosis of acute DVT was confirmed in all patients using venous Duplex US by a single experienced radiologist. Exclusion criteria included isolated infra-inguinal thrombosis, subacute or chronic DVT, terminal stage of malignancy with short life expectancy, pregnancy, or contraindications to contrast and thrombolytic agents.

## Procedure

The procedure was performed in a hybrid cardiovascular operating room. The patient was prone-positioned and popliteal vein or vena saphena parva vein was catheterized with a 6F sheath under the guidance of US. The ascending venography was performed. When complete obstruction of the vein revealed collateral circulation, the UACDT was performed using the Eko-Sonic Endovascular System (EKOS Corporation, Bothell, WA, USA). A hydrophilic guidewire (0.035-inch) (Terumo Corporation, Shibuya-ku, Tokyo, Japan) was placed through the sheath. In addition, a multi-lumen intelligent drug delivery catheter and matching US coaxial core wire were placed across the length of the target clot. A 40- or 50-cm length catheter was used for the thrombus length. After final positioning, the guidewire 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 equally 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), namely Alteplase (Actilyse, Boehringer Ingelheim GmbH, Germany), was given in a 5-mg bolus followed by an infusion at 0.02 mg/kg/h during the treatment. The 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, was automatically adjusted to optimize lysis of the treated segment. Thrombolysis was terminated, if complete clot lysis was achieved or the maximum infusion period of 56 h was reached. The adequacy of the venous inflow was evaluated by post-procedural venographic imaging study. Meanwhile, complete blood counts were checked every six hours. No inferior vena cava filter was used routinely to prevent pulmonary embolism before CDT treatment, except one patient due to a floating thrombus in the external iliac vein. Balloon angioplasty was performed successfully for >50% area reduction of the iliac vein in another patient.

### Follow-up

After the intervention, swelling and pain were evaluated in each patient. During the evaluation of swelling, we recorded limb circumferences in the calf at 10 cm below the tibial tuberosity at baseline and at 48 h after treatment.

The patients without additional problems were discharged with oral anticoagulant warfarin (Coumadin, 5mg; Zentiva Eczacıbaşı -İlaç \_ Sanayi ve Ticaret A.Ş., İstanbul, Turkey). Compression stockings were recommended to all patients for at least two years.

Post-procedural Duplex US was used to evaluate the vein patency and presence of venous reflux in the iliac and femoral veins. All patients were examined in the outpatient clinic through Duplex US at one month, six months, one year, and two years following the procedure.

### Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed in mean  $\pm$  standard deviation (SD). Categorical variables were expressed in number (n) and frequency (%). Paired samples t-test was used to evaluate calf circumference changing. A *p* value of <0.05 was considered statistically significant.

## RESULTS

The demographic and clinical characteristics of the

patients are shown in Table 1. The mean duration of the procedure was  $30.8 \pm 9.8$  (range, 19 to 56) h. The mean total Alteplase dose was  $42.4 \pm 7.9$  (range, 30 to 54) mg. The mean time from diagnosis to treatment was  $3.4 \pm 1.9$  (range, 19 to 56) days. The mean follow up was  $31.56 \pm 3.35$  (range, 25 to 37) months. Complete thrombolysis was successful in 88.9% (n=16) and in %11.1 (n=2) patients with partial clot lysis. In one patient, underlying lesions were successfully treated with balloon angioplasty. One bleeding at the catheter-insertion site were observed. No major peri-procedural complications such as pulmonary embolism or in-hospital mortality was observed. Immediate clinical improvement was observed in all patients. During follow-up, the mean calf circumference statistically significantly decreased from  $46.2 \pm 3.4$  cm to  $42.3 \pm 2.8$  cm at 48 hours ( $p < 0.001$ ).

Duplex US evaluation at one month, six months, one year, and two years after the procedure showed that the iliac vein patency rate was 100%; however, femoral vein insufficiency was found 5.6% (n=1), 11.1% (n=2), 16.2% (n=3), and 16.2% (n=3), respectively. No re-occlusion was observed in any patient.

## DISCUSSION

Our study results showed that UACDT was an effective and safe treatment strategy for acute iliofemoral DVT without popliteal vein thrombosis in the early and midterm. During follow-up, we also recommended oral anticoagulant therapy for at least six months and the use of compression stockings to our patients. We believe that standard treatment of DVT with UACDT is effective to maintain deep vein patency for selected patients.

The Society for Vascular Surgery (SVS) in conjunction with the American Venous Forum recommends early thrombus removal as the first line treatment method for acute iliofemoral DVT using percutaneous catheter-based techniques<sup>8</sup>. Early thrombus removal has been advocated to prevent PTS providing venous tract open and healthy venous valve competence<sup>9</sup>. Several studies have shown that CDT with or without an additional procedure such as US-accelerated, pharmacomechanic-assisted intervention is effective to obtain a dramatic reduction in the PTS incidence<sup>6,7,10,11</sup>. However, in their study, Kim et al.<sup>12</sup>

reported that CDT was unable to prevent PTS and its efficacy was controversial. In addition, the ATTRACT trial, a randomized-controlled trial, two-years results demonstrated that pharmacomechanical catheter-directed thrombolysis did not prevent PTS, increased the risk of major

bleeding, and did not influence the health-related quality of life or recurrent venous thromboembolism, although it improved leg pain and swelling over 30 days and reduced the severity of PTS<sup>13</sup>.

**Table 1. The demographic and clinical characteristics of the patients**

Patient number	Age	Sex	Clot location	Limb	Onset of symptoms (days)	Treatment time (hours)	Predisposing factor
1	72	M	EIV-CFV	R	2	24	Trauma-related immobilization
2	42	F	EIV-CFV-SFV	R	3	24	Unprovoked
3	67	F	EIV-CFV-SFV	L	7	28	Unprovoked
4	38	M	EIV	R	6	24	Oral contraceptive use
5	59	M	EIV-CFV-SFV	L	5	24	History of major surgery
6	72	F	CIV- EIV	R	4	32	Unprovoked
7	61	M	EIV-CFV-SFV	L	6	38	Unprovoked
8	25	F	EIV-CFV-SFV	R	4	48	Postpartum
9	54	M	CIV-EIV-CFV	R	2	24	History of major surgery
10	16	M	EIV-CFV-SFV	R	1	56	Hereditary thrombophilia
11	44	F	EIV-CFV-SFV	L	1	42	Unprovoked
12	48	M	EIV	R	1	36	trauma-related immobilization
13	44	F	EIV-CFV-SFV	R	2	28	Unprovoked
14	64	M	EIV-CFV-SFV	R	3	19	History of major surgery
15	64	M	EIV-CFV	R	2	24	History of major surgery
16	72	M	EIV-CFV-SFV	R	6	24	trauma-related immobilization
17	38	F	EIV-CFV-SFV	L	3	29	Postpartum
18	54	M	EIV-CFV	L	4	31	Unprovoked
Mean±sd	51.9±16.3				3.4±1.9	30.8±9.8	

Another controversial issue is US-assisted versus conventional CDT for acute iliofemoral vein thrombosis. Some studies have shown that UACDT is more effective and safe thanks to the mechanism of EKOS®, such as accelerated clot dissolution, reduced drug dosage, short treatment time, and low incidence of thrombolysis-related complications<sup>6,7</sup>. Recently, Engelberger et al.<sup>14</sup> published one-year results of their randomized-controlled trial and reported that additional intravascular US energy to conventional CDT had no positive or negative effect on the clinical or Duplex US outcomes in

patients who were treated for acute DVT. In another study, it was demonstrated that additional CDT was a cost-effective method in proximal DVT patients, compared to standard treatment alone<sup>15</sup>. Perrier et al.<sup>16</sup> also concluded that CDT should be performed for the patients ≤50 years old with extensive proximal DVT with a high risk of developing a severe PTS and low bleeding risk in terms of cost-effectivity<sup>16</sup>. A recently published review also supported the idea that CDT is a cost-effective method, particularly for patients with long life expectancy<sup>17</sup>. In present study, we demonstrated that UACDT was an effective method for acute iliofemoral DVT, particularly for patients with a

patent popliteal vein. Immediate clinical improvement was observed in all of our patients at 48 hours. In addition, two years after the intervention, the iliac vein patency rate was 100% with a femoral vein patency rate of 83.8%. However, we observed femoral vein insufficiency in three patients. These patients had femoral vein thrombosis at the time of diagnosis with a symptom of onset of six or seven days before the intervention. This finding suggests that early clot interval may affect the femoral vein valves contrary to expectations, as acute DVT period is defined as 14 days after the symptom onset. In the present study, the UACDT was performed very early period approximately  $3.4 \pm 1.9$  days after the symptom onset. It can be, therefore, considered that this is the reason why our primary lysis and vein patency rates were higher than the reported findings in the literature<sup>6,18</sup>.

Compression and anticoagulant treatment are the mainstay for acute DVT. Although the 9<sup>th</sup> edition of the Antithrombotic Guideline recommends routine use of compression stockings for two years after DVT to reduce the risk of PTS<sup>19</sup>, recent CHEST guideline has not recommended routine use of compression stockings due to the lack of evidences<sup>2</sup>. Although three patients had femoral vein insufficiency in our study, no PTS symptoms were observed. Compression stockings were used in all of the patients for two years. Compression stockings may not be effective to prevent PTS; however, we believe that it may be effective for preventing PTS symptoms. In a retrospective study, Kelley et al.<sup>20</sup> found no significant difference in the efficacy and safety of UACDT between the direct oral anticoagulants and vitamin K antagonists for VTE. According to the Antithrombotic Therapy for VTE Disease CHEST Guideline, anticoagulation therapy should be continued for at least three months after the CDT and non-vitamin K oral anticoagulants should be used rather than vitamin K antagonists for the treatment of DVT of the lower extremity in patients without any malignancy as long-term (first three months) anticoagulant therapy<sup>2</sup>. If the anticoagulation is initiated with vitamin K antagonist, drug should not be changed<sup>2</sup>. Although warfarin treatment has some disadvantages such as high number of foods and other drugs, requires dose adjustment with a narrow therapeutic range, and the presence of bleeding complications, it has been extensively studied for many years, as it is the most prescribed

anticoagulant drug. In a retrospective study, the success rate of warfarin treatment at the therapeutic level (INR = 2-3) was found to be 62.7%<sup>21</sup>. In our study, we used warfarin in all patients after UACDT. The INR level of the study population was maintained at 2 to 2.5. None of the patients experienced any complication.

Bleeding is the most common complication of thrombolytic agents. Systemic thrombolysis is associated with a high risk of serious bleeding complications, such as 3 to 6% risk of intracranial hemorrhage<sup>22</sup>. On the other hand, DVT is associated with lower bleeding rates, compared to systemic thrombolysis due to reduced dose of the thrombolytic agents and local application to the clot<sup>8</sup>. Venous access site bleeding is usually observed during CDT, while intracranial bleeding rarely occurs<sup>23</sup>. In our series, we observed no major bleeding complications in any patients. Only one puncture site bleeding was observed which was stopped with compression. To avoid any puncture site complication, we suggest that the insertion site of the catheter must not be traumatized and US must be used during catheterization. In our study, we observed no complication such as bleeding and hematoma at the insertion site in the early postoperative period. Furthermore, vena cava filter is not recommended for VTE under anticoagulant therapy<sup>2</sup>. Avgerinos et al.<sup>24</sup> suggested that vena cava filters during thrombolysis should be used in selected patients such as those with preoperative clinical pulmonary embolism symptoms and in women and potentially in patients with multiple risk factors for DVT. On the other hand, Protact et al.<sup>25</sup> reported that CDT for lower extremity DVT without prophylactic inferior vena cava filter placement was a safe and effective method. However, the aforementioned authors suggested that vena cava filter placement should be used selectively rather than routine procedure. In the present study, we inserted vena cava filter in only one patient due to a floating thrombus in the external iliac vein. Also, we did not observe pulmonary embolism during UACDT in our study population.

Nonetheless, there are some limitations to this study. The major limitation is the small sample size (only 18 patients). It can be attributed to the fact that the patients were selected carefully to perform UACDT in our clinic. We believe that the popliteal vein outflow prove the femoral and iliac vein

patency at the late period of iliofemoral DVT and CDT is not effective for iliofemoral DVT with popliteal vein thrombosis in the mid- or long-term. In addition, despite the retrospective nature of the study, patients' data were collected prospectively. Another limitation is that the patients were not screened for PTS during follow-up according to a standardized scoring system, such as the Villalta scoring system. However, none of the patients reported any complaint relevant to PTS symptoms during follow-up. Furthermore, we were unable to compare patients receiving standard therapy of DVT with an alternative technique for thrombus removal; therefore, we were unable to perform any statistical comparisons. Although the presentation of the results of a single technique might have affected our evaluation process, these findings still contribute to the literature in terms of midterm results of the UACDT for acute iliofemoral DVT without popliteal vein thrombosis.

In conclusion, our study results suggest that UACDT is a safe and effective method for carefully selected patients with acute iliofemoral DVT without popliteal vein thrombosis. In addition, UACDT may prove venous valve competence and prevent PTS through effective clot burden reduction in the early period of iliofemoral DVT. However, large-scale, long-term, randomized studies are needed to establish a definite conclusion and to prevent sequelae of DVT with the most optimal technique.

**Yazar Katkıları:** Çalışma konsepti/Tasarımı: EK, CSÜ; Veri toplama: EK, AK, EÇ; Veri analizi ve yorumlama: EK, CSÜ, AK, EÇ; Yazı taslağı: EK, CSÜ, AK, EÇ; İçeriğin eleştirilme: EK, CSÜ, AK, EÇ; Son onay ve sorumluluk: EK, CSÜ, AK, EÇ; Teknik ve malzeme desteği: -; Süpervizyon: EK, CSÜ, AK; Fon sağlama (mevcut ise): yok.

**Bilgilendirilmiş Onam:** Katılımcılardan yazılı onam alınmıştır.

**Hakem Değerlendirmesi:** Dış bağımsız.

**Çıkar Çatışması:** Yazarlar çıkar çatışması beyan etmemişlerdir.

**Finansal Destek:** Yazarlar finansal destek beyan etmemişlerdir.

**Yazarın Notu:** Çalışmanın bir kısmı Nisan 2018'de 14. Uluslararası Antalya Kardiyoloji ve Kalp Damar Cerrahisi Kongresi Güncellemesinde sözlü sunum olarak sunulmuştur.

**Author Contributions:** Concept/Design : EK, CSÜ; Data acquisition: EK, AK, EÇ; Data analysis and interpretation: EK, CSÜ, AK, EÇ; Drafting manuscript: EK, CSÜ, AK, EÇ; Critical revision of manuscript: EK, CSÜ, AK, EÇ; Final approval and accountability: EK, CSÜ, AK, EÇ; Technical or material support: -; Supervision: EK, CSÜ, AK; Securing funding (if available): n/a.

**Informed Consent:** Written consent was obtained from the participants.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** Authors declared no conflict of interest.

**Financial Disclosure:** Authors declared no financial support

**Acknowledgement:** Part of the study was presented as oral presentation at 14th International Update in Cardiology and Cardiovascular Surgery Congress, Antalya, Türkiye. April 2018

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