Tepecik Eğit. ve Araşt. Hast. Dergisi 2020;30(3):281-7
doi:10.5222/terh.2020.04557

Catheter-Directed Thrombolysis and Endovascular Therapy in Patients with Deep Vein Thrombosis: Early-Term and First Year Results

Derin Venöz Tromboz Tanılı Hastaların Kateter Yönlendirmeli Tromboliz tedavisi ile Endovasküler Tedavisi: Erken Dönem ve Birinci Yıl Sonuçları

Özgün Araştırma
Research Article

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ABSTRACT

Objective: *Deep vein thrombosis leads to post- thrombotic syndrome in the long term. The risk of developing a post-thrombotic syndrome increases when anticoagulation is the only treatment. Methods of catheter-directed thrombolysis were developed because of the high bleeding risk of systemic thrombolytic therapy. Along with hybrid approaches catheter-directed thrombolysis aims to reduce the frequency of post-thrombotic syndrome. We retrospectively report the early and follow-up results of our patients in whom we performed catheter-directed thrombolysis.*
Method: *Thirty-one patients aged 23-87 years had been diagnosed with acute proximal deep vein thrombosis (≤15 days' duration). Catheter-directed thrombolysis and if needed stent implantations were performed successfully. The patients who had a thrombosis of the inferior vena cava also underwent the placement of a vena cava filter. Patients were evaluated at 1, 6 and 12 months. Villalta scores were also determined for the diagnosis of post- thrombotic syndrome.*
Results: *Nineteen patients had a thrombus in the iliofemoral vein. The thrombus was extending to the inferior vena cava in six patients. In 12 patients the thrombus was in the femoropopliteal vein. Six patients whose thrombus extended to the inferior vena cava, underwent venous filter placement. In five of the patients with iliofemoral-thrombus, intraoperative control venography revealed iliac stenosis. This stenosis was treated with iliac stent implantation. Clot lysis was complete (>90% lysis) in twelve, partial (50-90% lysis) in seven of the 19 iliofemoral-thrombus patients. Ten femoropopliteal-thrombus patients achieved a complete and two a partial clot-lysis. There was minor bleeding in two patients. Major bleeding was not reported.*
Conclusion: *Catheter-directed thrombolysis reduces the frequency of post- thrombotic syndrome. Residual venous obstruction after catheter-directed thrombolysis should be treated by balloon dilatation/stent implantation to prevent re-thrombosis. We believe that treatment with a hybrid approach may be more effective in protecting patients from post- thrombotic syndrome.*

Keywords: *Catheter-directed thrombolysis, deep vein thrombosis, post-thrombotic syndrome, stent implantation*

ÖZ

Amaç: *Derin Ven Trombozu uzun dönemde posttrombotik sendroma yol açamaktadır. Uygulanan tedavi tek başına antikoagülan tedavi olduğunda posttrombotik sendrom gelişme riski önemli ölçüde artmaktadır. Sistemik trombolitik tedavinin yüksek kanama riskinden dolayı Kateter yönlendirmeli tromboliz yöntemleri geliştirilmiştir. Hibrid yaklaşımlarla birlikte Kateter yönlendirmeli tromboliz, posttrombotik sendrom sıklığını azaltmayı amaçlamaktadır. Biz bu çalışmada Kateter yönlendirmeli tromboliz tedavisi uyguladığımız hastaların erken dönem sonuçlarını ve birinci yıl takip sonuçlarını retrospektif olarak bildiriyoruz.*
Yöntem: *31 hastanın(23-87 yaş aralığında) hepsine akut proksimal venöz trombozu (≤15 gün) tanısı konmuştu. Bu hastalara Kateter yönlendirmeli tromboliz ve gerekirse stent implantasyonları sorunsuz olarak uygulandı. İnferior vena kava trombozu olan hastalara da vena kava filtresi yerleştirildi. Hastalar 1., 6. ve 12. aylarda Doppler ultrasonografi ile değerlendirildi. Posttrombotik sendrom tanısı için Villalta skorları da belirlendi.*
Bulgular: *Hastaların 19'unda iliofemoralde trombüs vardı. Bu hastaların altısında trombüs inferior vena kavaya uzanıyordu. Diğer 12 hastada trombüs femoropopliteal idi. Trombüsü vena kavaya uzanan altı hastaya venöz filtre yerleşimi uygulandı. İliofemoral trombüs hastalarının beşinde intraoperatif kontrol venografi esnasında iliyak darlık saptandı. Bu darlık iliak stent implantasyonu ile tedavi edildi. 19 iliofemoral trombüs hastasının onikisinde pıhtı lizisi tamamen (>% 90 lizis) ve yedisinde kısmen (% 50-90 liziz) idi. Femoropopliteal trombüsü olan hastaların onunda tam ve ikisinde kısmi pıhtı lizisi görüldü. İki hastada minör kanama vardı. İşlem sırasında ve sonrasında majör kanama bildirilmedi.*
Sonuç: *Kateter yönlendirmeli tromboliz, posttrombotik sendrom sıklığını azaltmaktadır. Kateter yönlendirmeli tromboliz sonrası rezidüel venöz tıkanıklık, erken dönemde trombozu önlemek için, balon dilatasyonu ve/veya stent implantasyonu ile tedavi edilmelidir. Hibrit bir yaklaşımlı bir tedavinin, hastaları posttrombotik sendromdan korunmasında daha etkili olabileceğine inanıyoruz.*

Anahtar kelimeler: *Kateter yönlendirmeli tromboliz, derin venöz tromboz, posttrombotik sendrom, stent implantasyonu*

Received/Geliş: 21.05.2020
Accepted/Kabul: 29.07.2020
Published Online: 05.01.2021

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Cite as: Abud B, Karaarslan K, Yıldırım MU, Albayrak G, Aykut K. Catheter-directed thrombolysis and endovascular therapy in patients with deep vein thrombosis: Early-term and first year results. Tepecik Eğit. ve Araşt. Hast. Dergisi. 2020;30(3):281-7.

INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) are common and preventable diseases. The incidence of venous thromboembolism is 1-2 per 1000 person-years. Proximal DVT involves the popliteal, femoral and iliac veins. It often causes PTE and post-thrombotic syndrome (PTS) [1]. In one-third to one-half of the patients with proximal DVT, PTS develops within one year, despite standard anticoagulant treatment [2]. PTS causes chronic deep vein insufficiency or venous stenosis. New endovascular treatments aim to reduce frequency and severity of PTS through recanalization of the deep veins [3]. Various treatment methods exist for use in DVT treatment. These treatments are anticoagulation only, catheter-directed thrombolysis (CDT), thrombectomy by mechanical aspiration and surgical thrombectomy procedures. CDT allows achieving a reduction in the incidence rates of PTS and venous obstruction [4,5]. In this study we retrospectively report early and the first- year follow-up results of our patients in whom we performed CDT.

MATERIAL and METHODS

In our study 31 patients (12 women and 19 men) with iliofemoral or femoropopliteal DVT were treated by CDT. The median age of the patients was 51 years (range, 23-87). Twenty-three thromboses were left sided and eight thromboses were right sided (Table 1). Demographic data and clinical results were analyzed. The diagnosis of DVT was achieved with the help of Doppler ultrasound (USG) and clinical findings. All had been diagnosed with acute DVT of ≤15 days' duration. All patients were informed about the procedure, the associated risks and benefits and gave informed written consent. Our study was conducted in accordance with the principles of Helsinki Declaration and consent was obtained from all patients for the study. The diagnosis of DVT was confirmed in all patients by a venography at the time of catheter insertion. All patients underwent CDT. Tissue plasminogen activator (tPA) treatment was administered after the procedure and a control venography was performed after this treatment. Stents were implanted to the stenosis identified in iliac regions. Doppler USG follow-up was performed on the first, sixth, and twelfth months and vein patency (chronic obstruction or chronic venous disease, the presence of thrombus, complete (>90% lysis) or partial (50-90% lysis) recanalization) was recorded. Reflux in the femoral and popliteal veins was determined. Reflux was defined pathologically, if it persists for more than 1 sec in the femoral vein and longer than 0.5 sec in the popliteal and superficial veins [6,7]. The great and small saphenous veins were not evaluated as long as their function appeared to be normal in the inguinal area and the popliteal fossa.

Physical findings and symptoms were recorded and Villalta scale was determined for each patient. Villalta scoring system declares the severity of disease with five lower extremity symptoms; which are pain, heaviness, cramps, pruritus and paresthetic neurologic disorder, and six clinical signs that includes skin induration, edema, venous ectasia, redness, hyperpigmentation and lower extremity pain that triggered with calf compression. Villalta scoring system uses a score between 0 and 3 which scales up with the severity of the PTS recorded during the examination. If a venous ulcer presented during the couse of disease it was recorded. A score of 5 or higher, or presence of venous ulcer at one of the follow-up assessments was accepted as indicating the presence of PTS [8].

Thrombolytic Treatment

The patients were placed in prone position on the angiography table. Following local anesthesia, a vascular introducer sheath was inserted from either the distal popliteal vein or the proximal small saphenous vein. Contrast agent was administered to obtain lower extremity venograms.

We used the EKOS device (EKOS, WA, USA) for CDT. We placed a 5.2F multi-lumen intelligent drug delivery catheter and matching coaxial core wires over a 0.035-inch guidewire along the length of the target clot. After application of a local anesthetic, we inserted a 7F introducer sheath into the distal popliteal or the proximal small saphenous vein under Doppler USG. The thrombosed venous segment was passed with a 5F vertebral hydrophilic catheter and hydrophilic guidewire. We positioned the catheter tip against the proximal end of the thrombus and then we replaced the guidewire with a microsonic core, which contains a series of ultrasound transducer elements. These ultrasound transducer elements are distributed approximately 1 cm apart along its leading tip, to deliver the ultrasound energy radially along the coaxial infusion zone. We primed the infusion catheter with a bolus of tissue plasminogen activator (tPA (alteplase)). After that a continuous slow infusion of tPA was then performed through the delivery side holes at a rate between 0.5 mg/h and 2 mg/h. Normal saline, 35 mL/h, was simultaneously administered through the central lumen as a coolant. Simultaneously ultrasound energy was delivered through the core. Patients also received continuous intravenous infusion of heparin through the introducer sheath. Heparin dosage was adjusted to achieve an activated partial thromboplastin time (aPTT) approximately 1.5 to 2.5 times the normal value. Heparin delayed new clot formation around the catheter. tPA (alteplase) administration was performed over 18-24 hours. The duration was shortened if fibrinogen levels were less than 150 mg/dL. Follow-up bedside ultrasound was performed in all patients daily.

We placed a vena cava filter in patients who had a free thrombus in the inferior vena cava. Patients with a ≥50% iliac vein stenosis underwent stent implantation.

Statistical Analysis

All data obtained from study were analyzed with Statistical Package for the Social Sciences 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous and categorical variables were expressed as percentages.

RESULTS

Nineteen out of 31 patients, had a thrombus in the iliofemoral vein. In six of these patients, the thrombus was extending to the inferior vena cava. In the other 12 patients the thrombus was in the femoropopliteal vein (Table 1). Six patients whose thrombi extended into the inferior vena cava underwent venous filter placement. In five of the iliofemoral thrombus patients, intraoperative control venography revealed an iliac stenosis. This stenosis was treated with iliac stent implantation (Table 2). Clot

Table 1. Patient characteristics.

Age(years) (IQR)	51 (23-87)
Sex F/M (n) (%)	12/19 (38.7/61.3)
DVT Side (n) (%)	
Left	23 (74.2)
Right	8 (25.8)
Localization (n) (%)	
Iliofemoral DVT	19 (61.3)
Femoropopliteal DVT	12 (38.7)
Wells risk criteria (n) (%)	
Advanced age	3 (9.7)
Prolonged immobility	6 (19.4)
Obesity	3 (9.7)
Recent surgery	7 (22.6)
History of major trauma	6 (19.4)
Idiopathic	6 (19.4)

IQR: Interquartile range; F: Female; M: Male; DVT: Deep vein thrombosis

Table 2. Operative outcomes.

IVC filter placement (n) (%)	6 (19.4)
Iliac stent implantation (n) (%)	5 (16.1)
Clot lysis	
Iliofemoral DVT (n) (%)	
Complete (>90% lysis)	12 (63.2)
Partial (50-90% lysis)	7 (36.8)
Femoropopliteal DVT (n) (%)	
Complete (>90% lysis)	10 (83.3)
Partial (50-90% lysis)	2 (16.7)
Death (n) (%)	0 (0.0)
Bleeding (n) (%)	
Major	0 (0.0)
Minor	2 (6.5)

IVC: Inferior vena cava; DVT: Deep vein thrombosis

lysis was complete (>90% lysis) in twelve and partial (50-90% lysis) in seven of the 19 patients with iliofemoral thrombi. Among the patients with a femoropopliteal thrombus, ten cases achieved a complete and two a partial clot lysis. No deaths occurred in our patients. In two patients' small acute hematoma occurred in the popliteal fossa, which didn't need treatment (Table 2). When we evaluated first year Villalta scores, one patient had venous ulcer and one patient had a score of 17. Thus two patients had severe PTS. One patient had moderate PTS, two patients had mild PTS and twenty-six patients had not any PTS. In five patients deep reflux was determined in the femoral vein and in two patients in the popliteal vein. One patient had reflux in both the femoral vein and the popliteal vein (Table 3). After one-year follow-up PTS was absent in 90.9% of the complete and 66.7% of the patients with partial lysis. In our study, complete lysis was observed in 83.9% of the patients in our study (Table 4).

Table 3. Postoperative follow-up characteristics.

	Iliofemoral DVT patients (n=19)	Femoropopliteal DVT patients (n=12)
Villalta Score		
< 5 (absent of PTS) (n) (%)	15 (78.9)	11 (91.7)
5-9 (mild PTS) (n) (%)	2 (10.53)	0 (0.0)
10-14 (moderate PTS) (n) (%)	0 (0.0)	1 (8.3)
≥15 (severe PTS) (n) (%)	1 (5.3)	0 (0.0)
Venous ulcer (n) (%)	1 (5.3)	0 (0.0)
Deep reflux (n) (%)		
Femoral vein	3 (15.8)	2 (16.7)
Popliteal vein	1 (5.3)	1 (8.3)
Femoral + popliteal vein	1 (5.3)	0 (0.0)
Recurrent DVT (n) (%)	0 (0.0)	0 (0.0)

PTS: Postthrombotic Syndrome; DVT: Deep vein thrombosis

Table 4. Correlation between lysis grade and PTS.

Absent of PTS (n) (%)	
Complete (>90%) lysis patients (n=22)	20 (90.9)
Partial (50-90%) lysis patient (n=9)	6 (66.7)
Totally (n=31)	26 (83.9)

PTS: Postthrombotic Syndrome

DISCUSSION

DVT is an important health problem. Especially proximal DVT which involves the popliteal, femoral and iliac veins, often causes PTE, phlegmasia cerulea dolens (PCD) and PTS. It leads to PTE and PCD in the short term and, to PTS in the long term [1]. Risk factors for proximal DVT are determined by Wells, and called "Wells criteria" [9]. Risk factors according to the Wells criteria were advanced age, prolonged immobility, obesity, recent surgery and history of major trauma in our patients. In 6 patients risk factors were not identified. These patients were considered as cases with diopathic DVT. The main therapy for DVT is a 3 to 6 months of anticoagulation therapy and elastic compression stockings for 2 years. Anticoagulant therapy is recommended to prevent prolongation, and recurrence of the thrombus, and PTE. Elastic compression stockings are recommended to prevent PTS [10]. However, the evidence for these recommendation is limited [11]. Anticoagulant therapy contributes to restrict thrombus propagation, prevents recurrence and PTE, but it does not achieve lysis of the clot and thus does not prevent PTS. The incidence of PTS after only anticoagulation therapy is between 40%-60% [12]. There are various methods of treatment for clot lysis in the treatment of acute DVT. These treatments are systemic thrombolysis, CDT, thrombectomy by mechanical aspiration and surgical thrombectomy procedures. The aim of these treatments is to restore the patency of venous lumen and to save the venous valves [13].

Systemic thrombolysis is effective in clot lysis. It involves intravenous injection of an agent which lysis clots. Systemic thrombolysis reduces also PTS and recurrence of DVT [14]. But hemorrhagic complications are highly prevalent in systemic thrombolysis [14,15]. CDT enables delivery of the thrombolytic agent through the target vessel, directly into the thrombus. Therefore, CDT reduces the total dose of thrombolytic agent required and minimizes the risk of bleeding. Studies reported incidence of 0-1% for intracranial bleeding in CDT, whereas its incidence was indicated as 3-6% in systemic thrombolysis [14-16]. According to the HAS-BLED scoring system major bleeding was not reported in our patients [17]. In two

patients, small acute hematomas developed in the popliteal fossa, which didn't need treatment. Several studies have reported the effectiveness of CDT in clot lysis and in restoring venous patency [14]. Clot lysis was complete (>90% lysis) in twelve and partial (50-90% lysis) in seven of our 19 iliofemoral DVT patients. In our patients with a femoropopliteal DVT, ten achieved a complete and two partial clot lysis (Table 3). CDT is also particularly useful in the prevention of PTS and of the recurrence of DVT. The possibility of PTS and recurrent DVT after CDT is directly correlated to the amount of residual thrombus after the procedure [18,19]. After one-year follow-up PTS disappeared in 90.9% in our complete lysis patients and 66.7% in our partial lysis patients. In our study total absence of PTS was seen in 83.9% of our patients (Table 4). Recurrent DVT was not seen in any of our patients.

PTS usually occurs within 3 to 6 months after the development of proximal DVT, but can be manifest even up to two years [20]. Up to 50% of the patients will show evidence of PTS two years after the development of a proximal DVT. PTS is a result of long-term venous hypertension. Venous hypertension is a result of venous obstruction, valve dysfunction and venous reflux. Clinically, the findings in PTS are those of lower extremity leg swelling and pain, heaviness, skin changes and venous claudication. The presence of venous ulcerations constitutes the most severe form of the syndrome [21]. We used the Villalta scoring system to make a diagnosis of PTS. At first, at sixth month and first year follow-up control visits, we recorded the physical findings and symptoms, and Villalta Scores were determined for each patient. Villalta scoring system declares the severity of disease with five lower extremity symptoms; which are pain, heaviness, cramps, pruritus and paresthetic neurologic disorder, and six clinical signs that includes skin induration, edema, venous ectasia, redness, hyperpigmentation and lower extremity pain that is triggered with calf compression. Villalta scoring system uses a score between 0 and 3 which scales up with the severity of the PTS recorded during the examination. If a venous ulcer presented during the course of the disease, then it was recorded. A total Villalta score of ≥15 or the presence of venous ulcer indicates severe PTS, a score of 10 to 14 identifies moderate PTS and a score between 5 to 9 defines development of mild PTS. A score lesser than 5 indicates that PTS does not exist. A score of ≥5, and presence of venous ulcer at one of the follow-up assessments was accepted as indicating the presence of PTS [8]. In our study, one patient had venous ulcer and one patient had a score of 17. Thus two patients had severe PTS. One patient had moderate PTS, two patients had mild PTS and twenty-six patients had no PTS.

The results of our study are consistent with previously published reports. In a randomized study of Enden et al., 50 patients treated with CDT were compared with 53 patients which were treated with standard treatment (anticoagulation + compression). They reported that CDT increased iliofemoral patency from 36% to 64%, six months after the procedure [22]. In another study, 101 patients (103 extremities) with acute iliofemoral DVT, CDT achieved satisfactory patency and function with 6 years of follow-up [23]. In a review of Chasey et al. [24] CDT decreased the incidence of PTS and venous obstruction. Few studies reported better results in patients treated with CDT + additional endovascular interventions (balloon dilatation or stent implantation) compared to CDT alone [25,26]. Additional endovascular intervention was used in five of our patients. In these patients intraoperative control venography revealed the presence of an iliac stenosis. This stenosis was treated with iliac stent implantation.

CONCLUSION

Proximal DVT leads to PTS in the long term. The risk of developing a PTS increases substantially when anticoagulation is the only treatment administered for DVT. CDT reduces the frequency of PTS and is safe

and promising. Residual venous obstruction after CDT should be treated by balloon dilatation and/or stent implantation to prevent early re-thrombosis. We believe that treatment with a hybrid approach may be more effective in protecting patients from PTS.

Limitations

Our study is a retrospective, observational study based on prospective data collection. It carries all the limitations of a retrospective study.

Acknowledgments

None

Author contribution statement

Abud B, Karaarslan K, Albayrak G and Yildirim M acted in every phase of this study. Aykut K made statistical analyses. Yildirim M, Aykut K contributed equally to this work.

Conflict of Interest: Informed Consent was obtained from all volunteers included in the study.

Funding: None of the authors have any financial relationship to disclose.

Informed Consent: Informed Consent was obtained from all volunteers included in the study.

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