Catheter-Directed Thrombolysis for Lower Extremity Deep Venous Thrombosis; Short Term Results of Catheter-Directed Thrombolysis for Deep Vein Thrombosis

Alt Ekstremite Derin Ven Trombozunda Kateter Aracılığıyla Trombolizin Erken Dönem Sonuçları

Evren ÖZÇINAR,[a]
Fatih GÖKALP[a]

[a]Clinic of Cardiovascular Surgery, Malatya State Hospital, Malatya

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Yazışma Adresi/*Correspondence:*
Evren ÖZÇINAR
Malatya State Hospital,
Clinic of Cardiovascular Surgery,
Malatya,
TÜRKİYE/TURKEY
evrenozcinar@gmail.com

ABSTRACT Objective: Thrombosis of the deep veins in the supragenicular region is a common clinical condition. Pharmacomechanical assisted removal of the thrombus for the initial management may provide the complete recovery with preservation of normal venous valve function. **Material and Methods:** Seventeen patients with deep vein thrombosis were treated using ultrasound-accelerated catheter-directed thrombolysis in addition to standard anticoagulant therapy. After 6 months, venous patency of the treated vessels was investigated using duplex ultrasound. **Results:** Thrombolysis was successful in 70.6% (12/17) of the patients. Twelve patients had complete clot lysis (>90% restored patency). Bleeding at the catheter-insertion site was observed in four patients. No pulmonary embolism was seen. In one patient, peroneal nerve injury occurred. **Conclusion:** Ultrasound-accelerated catheter-directed thrombolysis may be a promising treatment in patients with lower extremity deep vein thrombosis.

Key Words: Thrombolytic therapy; venous thrombosis; endovascular procedures

ÖZET Amaç: Supragenikuler bölgedeki derin ven trombozları sık karşılaşılan klinik olgulardır. Başlangıç tedavisi için farmakomekanik destekli trombusün ortadan kaldırılması, normal venöz kapakların korunması ile tam iyileşmeyi sağlayabilir. **Gereç ve Yöntemler:** Derin ven trombozu olan onyedi hastaya, standart antikoagülan tedaviye ek olarak ultrason destekli kateter aracılığıyla tromboliz uygulandı. 6 ay sonra, tedavi edilen damarların venöz patensisi dupleks ultrason ile incelendi. **Bulgular:** Tromboliz hastaların %70,6 (12/17)'sinde başarılıydı. Oniki hastada tamamen pıhtı erimesi (>%90 patensinin sağlanması). Dört hastada kateter girişim yerinde kanama gözlendi. Pulmoner emboli görülmedi. Bir hasta da, peroneal sinir hasarı gerçekleşti. **Sonuç:** Ultrason destekli kateter aracılığıyla tromboliz alt ekstremite derin ven trombozu olan hastalarda ümit verici bir tedavi olabilir.

Anahtar Kelimeler: Trombolitik tedavi, venöz tromboz, endovasküler prosedürler

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Deep vein thrombosis (DVT) of the lower extremity, a common cardiovascular condition with substantial morbidity and mortality, is estimated to affect 1-5% of the population in the world.[1] Patients with acute DVT are treated with anticoagulation, compression therapy, and mobilization. This standart therapy decreases mortality by preventing life-threatening pulmonary embolism (PE) and propogation of thrombosis, but has no direct thrombolytic effect.[2,3] Recanalisation and the preservation of normal venous valve function depending on the effectiveness of the patient's own fibrinolytic system resulted in high morbidity due to post-thrombotic syndrome (PTS).[4] Thus, there is a great need for improving the

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functional outcomes of the patients. Pharmacomechanical-assisted removal of the thrombus at the time of first presentation provides the best opportunity for complete recovery with preservation of normal venous valve function and avoidance of recurrent DVT and PTS. Meissner et al. have reported that valve function is more likely to be retained after early clot lysis.[5] Singh and Masuda have demonstrated that the combination of obstruction and reflux significantly increases the risk of developing PTS.[6]

Motarjeme[7] and Parik et al.[8] were the first to report ultrasound-accelerated (US-accelerated) catheter directed thrombolysis (CDT) in DVT. They reported the results of complete clot dissolution rates with US-accelerated CDT.[7,8] In vitro studies have demonstrated that high-frequency, low-power microsonic energy improves lysis of the thrombus considerably by increasing the uptake and penetration of thrombolytic drugs into the thrombus.[9] Therefore, US-accelerated CDT may also be a safe and promising option for immediate treatment of DVT.

The aim of this prospective study is to report the short-term results with emphasis on venous patency after 6 months of US-accelerated CDT in patients with DVT.

MATERIAL AND METHODS

PATIENTS

Between July 2011 and April 2012, 17 patients (10 males, 7 females) with a median age of 48 years (range 36-71) with symptomatic, duplex ultrasonograph (US) confirmed iliofemoral DVT, good functional status, acute thrombus formation (thrombus age<one month) and life expectancy exceeding 12 months were treated with US-accelerated CDT in Malatya State Hospital. Informed consent of the patients were obtained. Exclusion criteria for US-accelerated CDT were gastrointestinal bleeding or a cerebrovascular hemorrhage in the previous year, thrombus localization beyond the iliofemoral region, chronic thrombus formation (thrombus age>1 month), severe hypertension (>180/100 mmHg), active malignancy, surgery in the previous 6 weeks and/or pregnancy. Thrombolysis success was reported in 2 subgroups: Complete clot lysis was defined as >90% lysis (restored patency), and partial clot lysis (restored patency) of the initial thrombus, as assessed on the final US. Bleeding was classified as major, if it was overt with a fall in hemoglobin of ≥2 g/day, or when hemorhage led to tranfusion of ≥2 units of packed red blood cells (RBCs). Bleeding occurred in a critical organ (intracranial, retroperitoneal or pericardial) or, if it contributed to death, was defined as a major bleeding. Bleeding was classified as minor, if it occurred near the catheter insertion site.

All of the cases involved lower-extremity DVT. The proximal end of the thrombosis reached into the vena cava inferior in one, the iliac vein in four and the femoral vein in twelve cases. The age of thrombus (defined as the number of days between the onset of symptoms and the intervention) was 0-6 days (4/17), 7-13 days (5/17), 14-20 days (2/17) or ≥21 days (6/17) (Figure 1).

Eligible patients received US-accelerated CDT with recombinant tissue plasminogen activator (rtPA) combined with standard DVT therapy. Anticoagulation was given according to international guidelines (American College of Chest Physicians, 2012) with duration of planned treatment being 6 months for idiopathic DVT and 3 months provoked DVT.[1]

ANTITHROMBOTIC AND THROMBOLYTIC THERAPY

Before the CDT procedure, low-molecular-weight heparin (LMWH) was discontinued for at least 8

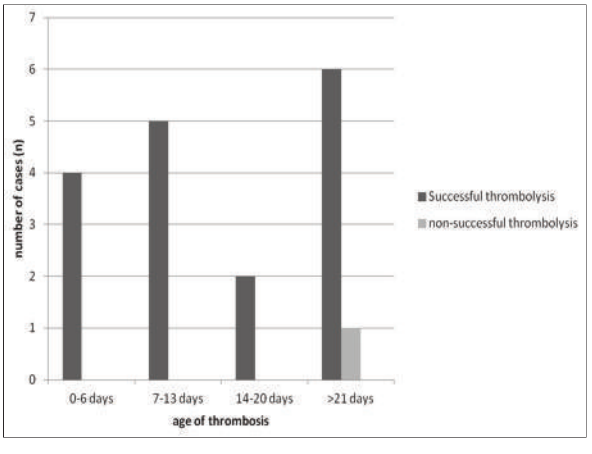

FIGURE 1: Age of thrombus versus success of thrombolysis. Successful thrombolysis includes complete and partial clot lysis, defined as >90% and 50-90% restored venous patency respectively.

hours, and oral anticoagulants were discontinued to obtain an INR <1.5. At the start of CDT, an intravenous bolus dose of unfractioned heparin (UFH), 5000 U, was given followed by a continuous intravenous UFH infusion at 15 U/kg/h.

US-accelerated CDT was performed using the EKOS Endowave® system (EKOS Corporation, Bothell, WA, USA), which combines a targeted-drug delivery catheter with high-frequency, low-power US energy. This system uses a standard 0.035-inch guidewire to position the 5.2-F multi-lumen Intelligent Drug Delivery Catheter and matching coaxial core wires (with available treatment lengths ranging from 6 to 50 cm) across the length of the target clot. In all cases, the procedure was performed in an operating room. A 7-F sheath and a 0.035-in. hydrophilic guide wire (Terumo Corporation, Shibuya-ku, Tokyo, Japan) were placed with the assistance of US-guided popliteal venous puncture. After applying a local anesthetic, an intraducer was inserted into popliteal vein guided by US with the end of the catheter at the proximal end of the thrombus. The guide wire was then pulled out and replaced by the Microsonic core containing a series of US transducer elements (2 MHz, 0.45 W) distributed approximately 1 cm apart along its leading tip to deliver evenly US energy radially along the coaxial infusion zone.

After priming the drug lumens of the catheter with heparin (1000 IU), a single bolus of rtPA (5.0 mg) was administered by slow infusion. Then, continuous infusion of rtPA was initiated through the side-hole-delivery infusion catheter at a mean rate of 1 mg/h rtPA. Simultaneously, normal saline solution was infused as coolant through the central lumen of the catheter at a rate of 35 ml/h. Thus, US energy was delivered through the core wire with simultaneous infusion of the thrombolytic drug. All patients were treated with an additional continuous intravenous infusion of heparin through the introducer sheath, which was monitored by assessment of the activated partial thromboplastin time (aPTT). Heparin dosage was adjusted to obtained an aPTT ratio of 1.5-2.5. Follow-up ultrasonograms were performed at the bedside in all patients the next day and 24-h intervals thereafter.

Thrombolysis was terminated, if complete clot lysis was achieved or the maximum infusion period of 72 h was reached. Hourly and total infused rtPA doses and infusion times were recorded. A weight-adjusted full therapeutic dose of subcutaneous LMWH given twice daily was initiated 1 hour after removal of the catheter. Patients received their thrombolytic care at an intermediate care unit and remained hospitalised for one night after termination of thrombolytic treatment, if no complications occurred. After discharge, patients were followed up according to the international guidelines for DVT therapy.[1]

FOLLOW-UP

Every 3 months after discharge, all patients returned to the outpatient department for a follow-up visit, including clinical investigation and duplex US examination to evaluate the patency of treated vein segments and the extent of postthrombotic damage to the deep veins of the lower limb. At the clinical visit, every patient had a thorough ultrasound examination using a dupplex US. Venous patency of all venous segments were evaluated. Patency assessment of the veins included identification of chronic occlusions or chronic venous disease as indicated by the presence of old and echogenic thrombus, partial recanalization, thickened venous wall with an irregular flow in lumen, decreased compressibility, lack of phasicity with respiration.[10]

STATISTICAL ANALYSIS

Variables were expressed as mean±SD and categorical variables were expressed as percentages. Statistical analyses were performed using SPSS statistical software (version 16.0; SPSS Inc., Chicago, Illinois).

RESULTS

STUDY GROUP

Seventeen patients treated with CDT for acute suprapopliteal venous thrombosis were included in the study. Baseline characteristics of the 17 patients are presented in Table 1.

SUCCESSFUL THROMBOLYSIS

Percutaneous catheterisation was successful in 12 procedures. Twelve out of 17 procedures (70%) resulted in complete clot lysis (>90% restored patency). In one case, thrombolysis was not successful. The unsuccessful case involved a 69-year- old male patient. He developed DVT after orthopaedic surgery. Duration of the DVT symptoms were 23 days. The leakage from the popliteal vein led to pain and cramps. The dropfoot syndrome of left foot occurred due to the peroneal nevre injury. Figure 1 shows the age of the thrombus and the success of thrombolysis.

SHORT-TERM FOLLOW-UP

The mean follow-up period was 12 months (range 6-15). In this period, no further occlusion of the venous system occurred in the patients, who were discharged with a patent venous system. In the 69-year-old man with unsuccessful thrombolysis, the 3- and 6-month US follow up revealed recanalisation of the inferior vena cava. The iliac vein remained occluded. In this patient, leakage from the vein wall led to inadequate therapy, probably caused failure of treatment. Results of 6th month duplex US assessment of the patients were summarized in Table 2.

COMPLICATIONS

Four (4/17; 23.5%) bleeding complications occurred at the site of the catheter-insertion. No PE was diagnosed during or after the treatment. However, in one patient, the dropfoot syndrome occurred. The mechanism explaining this complication may be related to nerve damage during the infusion period due to the leakage from the popliteal vein.

TABLE 1: Characteristics of treatment group. Data are mean (SD) or n (%).

Demographics	Patients with Catheter-directed thrombolysis (n=17)
Age(years)	54.7(±15.3)
Male	10(58.8%)
Femoral deep vein thrombosis	12(70.5%)
Iliofemoral deep vein thrombosis	4(33.3%)
Duration of symptoms (days)	11.7(±10.3)
Surgery previous 3 months	3(17.6%)

TABLE 2: Duplex US assessment of veins 6 months after CDT therapy.

Variables	Catheter-directed thrombolysis (n=17) (%)
Iliofemoral patency	12(70.5%)
Functional venous obstruction	5(29.4%)
Femoral venous insufficiency	9(52.9%)
Pelvic vein echoic lumen	2(11.7%)
Pelvic vein wall thickening	2(11.7%)
Pelvic vein no flow	1(0.05%)
Femoral vein incompressibility	3(17.6%)
Femoral vein echoic lumen	5(29.4%)
Femoral vein wall thickening	7(41.1%)
Femoral vein no flow	1(0.05%)

DISCUSSION

Standard DVT treatment focuses on adequate anticoagulation to prevent PE and thrombus propagation. However, anticoagulation alone has no direct thrombolytic effect.[11] As a result, current DVT treatment often does not restore venous patency, and venous valves are permenantly damaged. The combination of venous obstruction and reflux significantly increases the risk of developing PTS.[12] Anticoagulation halts propagation and formation of new thrombus; however it does not remove existing clots. The degree of recanalization may not be sufficient for complete resolution of clinical symptoms.[13] Sherry described only 6% thrombus lysis with anticoagulation alone.[14] Therapy, which can remove the thrombus and restore venous patency, may prevent recurrent thrombosis and PTS. Early thrombolysis for acute DVT has been shown to deliver improved patient outcomes, such as reduced cost and symptoms.[15]

Our study confirms the promising results of CDT for the treatment of DVT. Most evidence regarding CDT for the treatment of DVT is derived from patient series without controls or cohort studies, and little evidence is available from randomized clinical trials.[5,6,8,11] In CaVenT study, CDT reduced functional venous obstruction from 49% to 20%, and additional CDT increased 6-months patency from 36% to 64% as compared with standard anticoagulation treatment.[4] Elsharawy and

Elzayat reported complete lysis in 72% patients after CDT in 35 patients.[12] Our study obtained 70.6% (complete dissolution) success rate and this highlights the feasibility and capability of the US-accelerated CDT. The degree of lysis was found as a significant predictor of early and continued patency. In cases of complete clot dissolution, 75% of veins remained patent after one year, compared with only 32% of veins in cases of insignificant (<50%) lysis.[2] Parikh et al.[8] and Mewissen et al.[17] have reported increased complete clot lysis rates. The speed of intervention in acute thrombotic events is of clinical importance as there is a potential for reversal of occlusion, relief of symptoms, and preservation of valve function. Current evidence suggests that the optimal window for DVT thrombolysis is within 14 days from onset of symptoms. However, there has been no formal definition of an acute or chronic DVT from a CDT perspective. Although better lysis rates may be established within a 14-day intervention, the patients with deep vein thromboses frequently have been misdiagnosed. Physicians may not be aware of patients symptoms, and the time interval between the initiation of treatment and the diagnosis may last longer. In our study, the cut-off time for intervention is one month due to these drawbacks.

Major bleeding complications have been reported in 11% of patients and 39% of these were at the puncture site of the catheter directed-thrombolysis.[2] We observed no PE in our patients during thrombolysis. Bleeding at the catheter insertion site occurred in four cases; however, these minor complications did not disturb the efficacy of the thrombolysis procedure. Hematoma after bleeding limited itself at the insertion segment, and disappeared after ten days. In one patient, due to the leakage from the popliteal vein, dropfoot syndrome of the left leg occurred. The symptoms were severe, and the examination revealed peroneal nerve injury. The CDT therapy stopped, and the patient's symptoms regressed. After six weeks, recovery of motor functions was seen.

In the last decade, several studies have shown that PTS developed in almost half of the patients in whom DVT was treated with anticoagulation therapy.[2,5] Recent studies using CDT or pharmacomechanical thrombolysis have shown that a more aggresive approach in thrombus removal may reduce postthrombotic morbidity compared with anticoagulation alone.[8,11-13] Iliofemoral DVT can be safely and effectively treated at presentation in most patients with CDT. In our study, femoral vein wall thickening was demonstrated in 41.1% of the patients and femoral vein echoic lumen was seen in 29.4% of the patients after 6 months. Previous studies also highlighted the evidence of reduced long-term venous hypertension and decreased incidence of PTS.[2,11-13] In US-accelerated thrombolytic devices, ultrasound thrombus disruption can be used to increase the surface area of fibrin, presumably reducing the dose of thrombolytic required and increasing the rate of lysis.[16] US is also shown to improve lysis efficiency behind venous valves where thrombus is more difficult to remove.[9] CDT with local delivery of thrombolytic to the thrombus produces more favorable results than standart therapy, with double venous patency rate at 1 year and approximately 80% overall success rate.[17]

Although most patients with DVT experience gradual resumption of their baseline quality of life (QOL) within first 4 months after a DVT episode, approximately 33% continue to experience QOL impairment that correlates closely with the development of PTS.[18] Because PTS symptoms are aggravated by standing or walking, many patients are forced to alter their daily activities to include periods of rest and/or recumbency. As a result, PTS causes major long-term QOL impairment; specifically, poorer physical function, general health and health perceptions, more severe role limitations, and impaired social function. Importantly, even patients classified as having mild to moderate PTS exhibit scores that are lower than those of age-matched controls with DVT on QOL measures, so the QOL impairment caused by PTS does not appear to be restricted only to patients with severe sequelae. Moreover, although the economic impact of PTS has not been precisely quantified, PTS was estimated to cause 12% of the new cases with chronic venous disease (direct cost $261 million) and venous ulcer (direct cost $153 million) that occur yearly in the United States.[18]

When CDT technique is used, long-term anticoagulation remains an essential treatment component to prevent propagation of any persisting clot, to improve symptoms, and prevent pulmonary embolism; however if used alone, it yields just 6% complete DVT lysis at 10 days.[19-21] After acute anticoagulation with heparin and thrombolysis, long-term LMWH, or warfarin is recommended. Duration should be for at least 3 months in the setting of transient risk factors, and at least 12 months in DVT recurrence.[1]

We are aware of the limitations of this study. This is a prospective study on 17 patients treated with CDT. Lack of a control group and the small study group may limit the outcomes. We believe that this small population may be representative for patients with DVT, who potentially benefit from CDT. In the future, prospective, randomized, and properly designed studies in patients with DVT may enlighten the optimal therapy options.

CONCLUSION

New thrombolytics and delivery devices continue to improve clot lysis and removal; however, the patient risk-to-benefit profile must always be considered before any technique is routinely used in practice. The use of CDT technique with iliofemoral venous thrombosis may be associated with reduced morbidity and better outcomes. However, randomised controlled trials are needed to evaluate the long-term benefit of endovenous thrombolysis in patients with acute DVT.

Conflict of Interest

Authors declared no conflict of interest or financial support.

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