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Original Article

The effects of pharmacomechanical thrombolysis treatment administered to patients with iliofemoral deep vein thrombus

Serif Yurt, Oruc Alper Onk

Erzincan Binali Yıldırım University Mengücek Gazi Training and Research Hospital, Department of Cardiovascular Surgery, Erzincan, Türkiye

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Abstract

Aim: In this study, the mid-term results of the pharmacomechanical thrombolysis treatment administered in patients with iliofemoral acute-subacute (patients with symptoms less than 21 days old whose DVT was diagnosed with physical examination and duplex ultrasonography) deep vein thrombus (DVT) were investigated. The cases were evaluated in terms of disease-related quality of life, and the presence of post-thrombotic syndrome (PTS) which occurred in patients after previous DVT and treatment, and if present, its severity was determined.

Material and Methods: Disease-related status of 40 patients (24 males, 16 females; mean age 44; age interval 20-80 years) treated due to iliofemoral acute-subacute DVT with interventional method between July 2013 and January 2017 were retrospectively analyzed two years after the interventional treatment. These patients were considered as mid-term patients. The patients were evaluated with VEINES-QOL/Sym quality of life scale and the Villalta scale. The occurrence and severity of PTS, the presence of venous ulcer, and the diameter difference between legs were evaluated.

Results: No venous ulcer was present in our cases. In the evaluation made with Villalta scale, PTS was not observed in 20 out of 40 cases, mild PTS was found in 15, moderate PTS in 4, and severe PTS was observed in 1 case.

Conclusion: We have concluded that pharmacomechanical thrombolysis treatment administered in well-selected patients reduced the severity of PTS and increased the quality of life associated with disease in DVT treatment.

Keywords: Acute-Subacute deep vein thrombus, post-thrombotic syndrome, Villalta scale, venous insufficiency epidemiological and economic study quality of life/symptoms scale, pharmacomechanical thrombolysis

INTRODUCTION

Deep vein thrombosis (DVT) refers to vascular occlusion and interruptions in blood flow in deep veins induced mostly by thrombi in the lower extremity deep veins [1]. The average person/year annual incidence of venous thromboembolism is approximately 104-183 per 100.000 [2]. Iliofemoral DVT is the most serious form of venous thrombus and causes severe PTS. Previous studies have indicated that severe PTS develops

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Corresponding Author: Serif Yurt, Erzincan Binali Yıldırım University Mengücek Gazi Training and Research Hospital, Department of Cardiovascular Surgery, Erzincan, Türkiye
Email: yurt_serif@hotmail.com

in proximal DVT patients who are administered anticoagulant (AC) treatment alone [3]. The purpose of DVT treatment is to prevent pulmonary embolism (PE) and PE-associated death, to reduce DVT recurrence, and to minimize the occurrence of post-thrombotic syndrome (PTS) and severity of PTS [4]. Venous ulcer has been reported to occur in 15% of the patients within five years. Current prospective studies have revealed that proximal DVT is an independent risk factor for the formation of PTS [4].

PTS is the most important long-term complication of acute DVT, although not as dramatic as PE. PTS is diagnosed by interpreting the symptoms and objective clinical findings of patients with DVT and by making clinical scores. PTS develops in approximately 25-50% of the patients with first-episode iliofemoral DVT [4]. AC treatment alone is insufficient to reduce the risk of PTS formation and severity of PTS. It has been noticed in randomized studies that the results of patients treated with thrombus removal strategies are better rather than the ones treated with AC alone [5]. Interventional treatments in proximal DVTs have been included into the literature by ACCP (American College of Chest Physicians) as a recommendation [6]. In our study, it was aimed to evaluate the patients administered with pharmacomechanical thrombolysis (PMCDT) treatment due to acute/subacute iliofemoral DVT in terms of their disease-related quality of life, and to determine whether PTS occurred in our patients subsequent to previous DVT and treatment and, if so, its severity.

MATERIAL AND METHODS

Clinical data

The study group included 40 patients (selected randomly through simple non-probable random sampling) administered with PMCDT method and hospitalized due to iliofemoral acute-subacute DVT (patients with symptoms less than 21 days old whose DVT was diagnosed with physical examination and duplex ultrasonography) in Erzincan Binali Yıldırım University Mengücekgazi Training and Research Hospital Cardiovascular Surgery clinic between July 2013 and January 2017. Follow-up information and phone numbers of the patients were obtained from the hospital data processing system. Treated patients were contacted by phone, informed about the study, and invited to our clinic to evaluate their current status after treatment with quality of life questionnaires. The criteria for exclusion from the study were determined as the patients' not being able to come to the hospital control, not volunteering to participate in the study, being older than 80 years old, and being younger than 20 years old. Our cases were informed about the research again and their verbal and written consents were obtained for the research. Subsequently, the questions in the culturally adapted VEINES-QOL/Sym scale and the questions in the Villalta scale and the evaluations were presented to our cases. The parameters related to the symptoms and signs were filled in completely. Our patients (interventional treatment was applied to patients who had a significant difference in diameter between the legs and who were thought to have a high thrombus burden) were evaluated for two years (23-26 months on average) after PMCDT treatment and were regarded as mid-term cases. Ethics committee approval was obtained from Erzincan University Clinical Research Ethics Committee (Issue: E.51785, Date: 16.11.2017). The study was carried out in accordance with the principles of the Declaration of Helsinki.

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Surgical technique

Before the treatment, the risks and advantages of the treatment were fully explained to our patients and their informed consent was obtained. The protocol we used for the cases was as follows: endovascular treatment was administered in the operating room and under local anesthesia. Before the procedure, 100-unit/kg heparin (Poliparin, Polifarma, Istanbul, Turkey) was administered intravenously to our cases and 10 mg alteplase (ACTILYSER Boehringer Ingelheim, Germany) was diluted with saline and infusion was started to be given; all of the cases were operated on the contralateral femoral vein with the Seldinger method under local anesthesia and a temporary vena cava filter (Aegisy, Lifetech Scientific Crop, Shenzhen, China) was placed under the renal vein with 0.035''(0.89mm), 260cm hydrophilic guidewire (APTMedical Inc., Hamburg,Germany) in order to reduce the possible risk of pulmonary embolism during the procedure; ultrasound-guided intervention was performed from the popliteal vein with the Seldinger method, 8-Fr sheath was placed and venography was administered; mechanical thrombolysis catheter the Cleaner thrombectomy device (Argon Medical Devices, Inc., Plano, TX, USA), that functions by auto rotating, helical-shaped, flexible wire within the vessel, was advanced to the inferior vena cava; maceration and fragmentation of the thrombus was performed from proximal to distal. Venography was administered again subsequent to the procedure; balloon angioplasty, 12 mm to iliac vein, 10 mm to femoral vein (Extender®, Invamed, Turkey) was performed for residual stenosis (for >70% stenosis), the sheath was removed, bleeding was controlled; the patients were taken to the intensive care unit until the end of the thrombolytic infusion, low molecular weight heparin (LMWH) (Clexane®, Sanofi Winthrop, Le Trait, France) and warfarin (Coumadin®, Zentiva, Istanbul, Turkey) were started, extremity elevation was administered, compression stockings were put on at 25-35 mmHg pressure, mobilization was promoted, and subsequently, the vena cava filter was removed when the INR level reached the treatment dose. There were no complications in our cases.

Coumadin treatment was administered for 6 months for provoked

DVTs and for 1 year for non-provoked DVTs. Early-period patients were called for weekly INR monitoring. In terms of PTS, the patients were called for control at the 6th, 12th and 24th month periods, and the control examinations were performed physically.

Venous Insufficiency Epidemiological and Economic Study Quality/Symptom Scale (VEINES-QOL/Sym)

The VEINES-QOL/Sym scale is a scale including 26 questions and 8 sections developed to evaluate the effects of venous diseases upon symptoms and quality of life by analyzing the perspectives of patients. The low scores indicate poor quality of life. The VEINES-QOL/Sym scale was found to be a reliable and valid method designed to be used in the follow-up of venous diseases by Lamping et al [7].

Çırak et al. investigated the cultural usability, reliability and validity of the VEINES-QOL/Sym quality of life scale in Turkey [8] and concluded that the Turkish version of VEINESQOL/Sym scale had perfect reliability and good adaptation with Turkish culture.

Villalta scale

It is possible to determine the presence and severity of PTS with clinical scoring systems. Villalta scale has been regarded to be the most appropriate scale for the diagnosis and grading of PTS among these clinical scorings in mutual studies [9]. Moreover, evaluating quality of life scales and Villata scale together provides more accurate results for the diagnosis of PTS [10]. Soosainathan et al. determined that the use of Villalta scale and the VEINES QOL/Sym quality of life scale together was better to evaluate PTS in patients rather than using the Villalta scale alone [10].

Statistical analysis

The data of the study were analyzed using IBM SPSS ver.18.0 (IBM Co., Armonk, NY, USA). The distributions were presented as percentage and average. The data were interpreted using the descriptive analysis method. Due to the limited number of cases, the comparisons between paired groups (age groups and gender groups) were performed with Mann-Whitney U-test as a nonparametric test. A p value less than 0.05 was considered statistically significant.

RESULTS

A total of 40 cases were included in the study. 60% of the cases were male and 40% were female. Demographical characteristics of the cases were presented in Table 1. The frequency for the patients to experience disease-related complaints was questioned in the first category of the VEINESQOL/Sym quality of life scale. The complaint of throbbing never occurred in 87.5% of our cases; the most common complaint was pain in the legs with the rate of 15%; there were no complaints at all in the vast majority of patients, and this was associated with high quality of life. Whether the cases experienced restrictions in their social relationships with their families and friends or not was analyzed as well. It was observed that there was no restriction in social activities in 57% of the cases. There were no patients who had excessive difficulty in social activities after the disease. 87.5% were uninfluenced or mildly influenced. These findings revealed that post-treatment quality of life was high. The level of leg pain in the last one month was analyzed. There was no leg pain in the last one month in 35% of our cases, and 2.5% of the cases were determined to have severe leg pain. It was determined that 92.5% of the cases had no pain, very mild pain, and mild to moderate pain. In this section, it was observed that our patients had high quality of life scores (Table 2). In terms of analyzing the disease-related psycho-mental state, only one patient was specified in the "always" parameter which indicated the worst quality of life. It was observed that an average of 53.5% of our cases had a high quality of life score (Table 3). In the comparison made between age groups, a significant difference ($p<0.05$) was found in the evaluation of complaints compared to one year ago (Table 4).

Table 1. Demographic characteristic of patients

Demographics and procedure details	n=40
Age (y)	72±10(30-80)
Gender	
Male	24(60%)
Famale	16(40%)
Etiology	
Idiopatic	8(20%)
Thrombophilia	4(10%)
Cancer	8(20%)
Bed rest	12(30%)
Hormone therapy	4(10%)
Post-surgery	4(10%)
Side of DVT[1]	
Right sided	12(30%)
Left sided	28(70%)
Additional endovascular treatment	
Balloon angioplasty	12(30%)
Stent placement	0(0%)
Anticoagulant therapy	
Warfarin	32(80%)
LMWH	8(20%)
Planned anticoagulant therapy period	
6 months	28(70%)
1 year	8(20%)
Lifelong	4(10%)

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Table 2. The level of leg pain experiencent in the last one month

The level of leg pain	n = 40
Never	14(35%)
Very mildly	9(22.5%)
Mildly	2(5%)
Modaretely	12(30%)
Severely	2(5%)
Very severely	1(2.5%)

Table 3. Disease-related pyscho-mental status

Pyscho-mental status	n = 40
Have you ever worried about the appearance of your legs?	
Always	0(0%)
Mostly	1(2.5%)
Often	1(2.5%)
Sometimes	4(10%)
Rarely	8(20%)
Never	26(65%)
Have you ever felt nervous?	
Always	1(2.5%)
Mostly	2(5%)
Often	4(10%)
Sometimes	16(40%)
Rarely	4(10%)
Never	13(32.5%)
Have you ever felt like you were a burden to your family and friends?	
Always	0(0%)
Mostly	2(5%)
Often	2(5%)
Sometimes	10(25%)
Rarely	5(12.5%)
Never	21(52.5%)
Have you ever worried about hitting something?	
Always	0(0%)
Mostly	5(12.5%)
Often	2(5%)
Sometimes	8(20%)
Rarely	8(20%)
Never	17(42.5%)
Have you ever worried about lumpy images on your legs?	
Always	0(0%)
Mostly	1(2.5%)
Often	1(2.5%)
Sometimes	3(7.5%)
Rarely	5(12.5%)
Never	30(75%)

Table 4. Analysis of parameters by age range

	Age	n	Rank avarage	Total	n	p
Symptoms	20-45	24	22.98	551.5		
	45-80	16	16.78	268.5	132.5	0.097
	Total	40				
Restriction	20-45	24	23.33	560		
	45-80	16	16.25	260	124	0.058
	Total	40				
Activity	20-45	24	21.77	522.5		
	45-80	16	18.59	297.5	161.5	0.378
	Total	40				
Perception	20-45	24	20.9	501.5		
	45-80	16	19.91	318.5	182.5	0.792
	Total	40				
Complaints	20-45	24	19.02	456.5		
	45-80	16	22.72	363.5	156.5	0.309
	Total	40				
Results	20-45	24	20.02	480.5		
	45-80	16	21.22	339.5	180.5	0.739
	Total	40				
Time	20-45	24	22.13	531		
	45-80	16	18.06	289	153	0.258
	Total	40				
Comprasion with a year ago	20-45	24	17.58	422		
	45-80	16	24.88	398	122	0.016
	Total	40				
Social restriction	20-45	24	18.17	436		
	45-80	16	24.00	384	136	0.08
	Total	40				
Pain level	20-45	24	17.85	428.5		
	45-80	16	24.47	391.5	128.5	0.067
	Total	40				
Presence of ulcus	20-45	24	20.5	492		
	45-80	16	20.5	328	192	1
	Total	40				

The symptoms were analyzed with the Villalta scale. 82.5% of our cases had no pain, and 82.5% had no complaints of numbness. The symptom with the most severe level of complaint was found to be itching with the rate of 10%. On average, 72.5% of our cases answered all complaints as "no complaints".

The symptoms of the patients were analyzed with the Villalta scale. Edema was considered to be severe in only 1 of our cases. There was no pain in 90% of our cases, no induration was observed in 87.5%, and no new venous ectasia was diagnosed in 85%. In the physical examinations performed at the 6th, 12th and 24th months, the difference in diameter between the legs persisted in only 1 patient (2.5%).

As a conclusion, PTS was not observed in 20 out of 40 cases, mild PTS formation was found in 15, moderate PTS was found in 4, and severe PTS was found in 1 case in the evaluation with Villalta scale.

DISCUSSION

In our study, the aim was to evaluate the mid-term status of patients administered with PMCDT treatment for acute/subacute iliofemoral DVT in terms of disease-related quality of life, and to determine whether PTS occurred in our patients subsequent to previous DVT and treatment, and if it did, its severity.

PTS was one of the devastating long-term complications of DVT. In this study, swelling in the leg, pain, feeling of heaviness in the leg, weakness in the leg, stasis dermatitis and venous ulcer were observed in patients. Despite adequate and appropriate AC treatment, PTS occurred at the rate of 40% in patients with symptomatic first attack DVT [4]. PTS frequently occurred in proximal DVTs. In our study, the rate of PTS was 50%.

AC treatment alone did not provide thrombolysis, stopped the progression of thrombus and reduced the frequency of recurrence. It was considered that the presence of residual thrombus caused the destruction of venous valves and chronic venous hypertension, and these factors led to PTS. Systemic thrombolysis provided significant thrombus resolution in the early period. However, routine clinical use was not recommended due to the fact that it caused side effects at an unacceptable level [11]. It was considered that providing thrombolysis in the early period reduced valve damage, chronic venous hypertension and subsequently, the incidence of PTS. In endovascular thrombolytic treatments, it was determined that more efficient thrombolysis was achieved with less thrombolytic agents rather than systemic thrombolytic therapy. There were further studies analyzing the effects of endovascular treatment protocols upon PTS formation. We evaluated our research in the light of these studies.

Interventional and surgical treatments were recommended as Grade B treatment by the AHA (American Heart Association) in massive proximal acute DVTs with low bleeding risk [12]. DVT patients were screened by Bauer in the 1930s, and these patients were evaluated 5 years after the previous DVT. While venous insufficiency was present in all patients, venous ulcer was encountered in 20% [13]. These high rates dramatically decreased with the inurement of AC agents in the 1940s [14]. There were differences between AC agents in terms of preventing and reducing PTS. Relatively less PTS was diagnosed in patients with DVT followed up with LMWH rather than the ones treated with vitamin K antagonists (VKA) [15]. It was thought that the anti-inflammatory effects of LMWHs could lead to this decrease. It was determined in the EINSTEIN study in which 3449 patients were screened that new generation oral anticoagulants (NGOAC) were not superior to VKAs in the formation of PTS [16]. In our study, treated patients were followed up with VKA.

Proximal DVT had a 2-fold increased risk factor for PTS when compared to distal DVT [17]. More invasive interventions can be needed to reduce the risk of PTS in proximal DVTs. It was found that early restoration of vein patency ("open vein" hypothesis) led to the recovery of valve function and decrease in the risk of PTS formation [18]. The thesis that interventional treatments can reduce the occurrence of PTS in acute/subacute proximal DVTs guided our study. Catheter directed thrombolysis (CDT), PMCDT and percutaneous mechanical thrombectomy (PMT) are among the interventional treatments used. CDT was used with imaged guided catheter placement to infuse thrombolytic agents directly to thrombosed vein. Therefore, this method can achieve a high intra-thrombus drug concentration, reduces the thrombolytic dose, reduces hospital stay, and reduces the risk of bleeding [18]. Ultrasound (US) – accelerated CDT is another treatment method. US waves increase the permeability of the thrombus by acting on the fibrin strands, thus facilitating the delivery of therapeutic agents into the clot [19]. The Ekosonic Endovascular System (Ekos, Boston Scientific, USA) is an US-accelerated thrombolytic system. Angiojet Rheolytic Thrombectomy Catheter (Boston Scientific, USA) is commonly used in the treatment of PMCDT. PMT device systems can remove clots, such as the Indigo System (Penumbra Inc., Alemada, Calif), the Arrow – Tretola (Telefex Inc., Limeric, Pa), the Aspirex S endovascular system (Straub Medical, Wangs, Switzerland). Multi-center, large-scale studies on this subject have been conducted and are continuing to be conducted.

The ATTRACT (acute venous thrombosis: thrombus removal with adjunctive catheter–directed thrombolysis) was a randomized controlled study including 56 centers. Whether PMCDT prevented PTS formation in acute proximal DVTs was analyzed in this study [20]. In the ATTRACT trial there was no significant difference in PTS incidence between CDT group and anticoagulation alone at 2-year follow-up, but, moderate-to-severe PTS was significantly lower in CDT group at 2-year follow-up Villalta score [TT]. The results of our study (PTS was not observed in 20 out of 40 cases, mild PTS formation was found in 15, moderate PTS in 4, and severe PTS was found in 1 case in the evaluation with Villalta scale) are similar to these results.

The Catheter–Directed Venous Thrombolysis (CaVenT) study was a multicenter, randomized controlled study. It analyzed the treatment of proximal acute DVT with CDT (Catheter-Directed Venous Thrombolysis) method. In this study, 2-year data of 189 patients with proximal DVT administered with AC treatment alone and CDT accompanied by AC treatment were analyzed. The clinical conditions of the patients were evaluated with the Villalta scale. PTS formation was found to be 14% less at the end of 2-year period in the group of patients treated with CDT [21].

Quality of life was found to be slightly better in the CDT treated group. A 28% decrease in the risk of PTS formation occurred in 42% of the patients treated with CDT. Interestingly, the severity of PTS in the patient group treated with CDT and the severity of PTS in the patient group administered only with AC treatment were found to be similar, as observed in the CDT treatment group while evaluating the 5-year results of the CaVenT study [22].

In the study of TORPEDO (Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion), the patients administered only with AC treatment subsequent to DVT and the ones who underwent percutaneous endovenous intervention were followed for 30 months and they were compared in terms of PTS occurrence. PEVI (percutaneous endovenous intervention) cases indicated the patients who underwent thrombectomy, CDT or PMCDT accompanied by stent implantation and/or balloon angioplasty. The patients were recommended to wear medium-high pressure 30-40mmHg external compression stockings (ECS) for at least 6 months. The incidence of PTS was found to be 29.6% in the patient group administered only with AC treatment. This rate was determined to be 6.8% in the PEVI group [23].

The BERNUTIFUL (BERN Ultrasound–enhanced Thrombolysis for Ilio-Femoral Deep Vein Thrombosis versus Standard Catheter Directed Thrombosis) was a randomized study carried out in 2015; CDT and ultrasound-accelerated catheter-mediated thrombolysis treatments were compared in terms of PTS formation, and no significant difference was found [24].

In the ACCP VTE guideline updated in 2016, CDT and PMCDT treatment methods were not recommended as first-step treatment in DVT. However, AHA, Society of Interventional Radiology, Society of Vascular Surgery and American Society of Venous Diseases reported that interventional treatment methods could be preferred in patients with well-selected acute iliofemoral DVT and low bleeding risk.

The most important limitations of this study is that it was conducted retrospectively in a single center and with limited number of patients.

CONCLUSION

When our cases were analyzed retrospectively, it was found that the disease-related quality of life scores were high. It was observed in the evaluation made with the Villalta scale that 50% of our cases did not have PTS, 37.5% had PTS at mild level, 10% had moderate level of PTS, and 2.5% had severe PTS. These rates were relatively lower than the PTS rates in patient groups treated with only AC drugs. In conclusion, we found that interventional treatments increased venous patency, prevented valve functions, reduced PTS formation and increased disease-related quality of life in patients with high risk of PE, proximal DVT, extremity vitality under threat, life expectancy longer than 6 months, symptom onset less than 21 days, and in patients who did not contraindicate thrombolytic therapy.

Ethics Committee Approval: Ethics committee approval was obtained from Erzincan University Clinical Research Ethics Committee (Issue: E.51785, Date: 16.11.2017).

Patient Consent for Publication: Individual informed consent was waived due to retrospective design.

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