The Efficacy and Safety of Pharmacomechanical Thrombolysis and Medical Therapy for Symptomatic Deep Venous Thrombosis

Semptomatik Derin Ven Trombozunda Farmakomekanik Tromboliz ve Tıbbi Tedavinin Etkinliği ve Güvenliği

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ABSTRACT Objective: To prospectively compare the efficacy and safety of pharmacomechanical thrombolysis (PMT) and medical therapy for symptomatic deep venous thrombosis (DVT). **Material and Methods:** Between January 2015 and July 2016, 69 patients with a history of lower extremity DVT symptoms less than 21 days were managed either with a rotational thrombectomy device (ReyaThrombectomy ® Biolas FG Grup, Ankara, Turkey) or medical therapy including anticoagulation and compression stocking. Degree of lysis, symptomatic relief and patency were analyzed. **Results:** Thirty-four (47.9.0%) of the patients had a ilio-femoral thrombosis. The mean duration of the symptoms was 6.8 (2-20) days. Fourty-four and twenty-five patients were managed with PMT and medical therapy, respectively. At the end of the PMT procedure, 36 patients (81.8%) had a complete (Grade III) thrombus resolution. Grade II lysis was noted in 8 (18.2%) of the patients. One patient developed access site hematoma. There was no mortality. At third month, the venous obstruction was observed in 7 (15.9%) and 11 (44%) of patients in PMT and medical therapy groups, respectively ($p<0.05$). There was a significant clinical improvement in PMT group as evaluated by clinical symptom score. (1.6 ± 0.8 vs. 2.1 ± 0.8, $p=0.02$). **Conclusion:** The rotational thrombectomy is safe, fast and more effective alternative to current medical therapy for the management of DVT.

Keywords: Deep venous thrombosis; rotational thrombectomy

ÖZET Amaç: Semptomatik derin venöz trombozunda (DVT) farmakomekanik trombolizin (PMT) ve medikal tedavinin etkinliğinin ve güvenilirliğinin prospektif olarak karşılaştırılması. **Gereç ve Yöntemler:** Ocak 2015 ile Temmuz 2016 tarihleri arasında, alt ekstremite DVT semptomları 21 günden az olan 69 hastaya rotasyonel trombektomi cihazı ile tedavi (ReyaThrombectomy ® Biolas FG Grup, Ankara, Türkiye) veya antikoagülan ve kompresyon çorabı içeren medikal tedavi uygulandı. Trombüsün erimesinin derecesi, semptomatik rahatlama ve açıklık analiz edildi. **Bulgular:** Otuz dört (%47,9) hastada ilio-femoral tromboz vardı. Belirtilerin ortalama süresi 6,8 (2-20) gündü. Kırkdört hastaya PMT ve yirmi beş hastaya medikal tedavi uygulandı. PMT işleminin sonunda, 36 hastada (%81,8) trombüste tam (Grade III) çözülme vardı. Hastaların 8 (%18,2)'sinde Evre II liziz saptandı. Bir hastada girişim yerinde hematom gelişti. Mortalite görülmedi. Üçüncü ayda PMT ve medikal tedavi gruplarında sırasıyla 7 (%15,9) ve 11 (%44) hastada venöz tıkanıklık görüldü ($p<0,05$). Klinik semptom skoru ile değerlendirildiğinde PMT grubunda belirgin bir klinik iyileşme vardı. ($1,6\pm0,8$ vs. $2,1\pm0,8$, $p=0,02$). **Sonuç:** Rotasyonel trombektomi, DVT tedavisinde güncel medikal tedaviye alternatif olarak güvenli, hızlı ve daha etkilidir.

Anahtar Kelimeler: Derin ven trombozu; rotasyonel trombektomi

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Deep venous thrombosis (DVT) is an important disease causing significant morbidity.[1] Over the past decade, Pharmacomechanical approaches have emerged as an effective alternative to anticoagulant

therapy in patients with acute DVT.[2] While several observational studies have demonstrated the successful application of PMT, no multicenter, randomized controlled trials have yet demonstrated benefit of this therapy.[3,4]

Several PMT devices have been developed over the past two decades.[4,5] The ReyaThrombectomy (Biolas) thrombectomy device (FG Grup) is a battery-operated hand held, percutaneous mechanical thrombectomy device allowing the clot to be macerated and aspirated through an introducer sheath. Therefore, the aim of this prospective study was to evaluate the efficacy and safety of pharmacomechanical thrombectomy by comparing medical therapy for the treatment of DVT.

MATERIAL AND METHODS

PATIENTS

Following institutional review board approval, consecutive patients with symptomatic lower extremity DVT in a two-year period between January 2013 and July 2014 were admitted. Data were prospectively collected for the demographics, indications for treatment, periprocedural complications, clinical outcomes, and follow-up with duplex ultrasound imaging that was reported according to the Society of Interventional Radiology (SIR) reporting standards for the endovascular treatment of lower-extremity DVT.[6]

Patients with a history of DVT symptoms less than 21 days were included in this prospective cohort. At the time of inclusion, each patient underwent a careful clinical evaluation by the consulting physician and a standard checklist was filled out, including risk factors for venous thromboembolism and signs and symptoms of DVT. Patients were evaluated by leg circumference and clinical symptom scale which includes six symptoms (leg swelling, pain, pitting edema, erythema, paraesthesia and limitation in physical functions). Each symptom was rated as 0 (absent) or 1 (present). The points were then added to determine the total score. The diagnosis of DVT was made in all of the patients using by venous duplex imaging.

The patients consisted of 45 men and 24 women. The mean age was 48.4±16.8 years (range, 20 to 60 years). This is a prospective cohort study, not a randomized trial. PMT or medical therapy group assignment was decision of senior author. The patients who did not meet the inclusion criteria for PMT did not undergo PMT and they were assigned to medical therapy group. Patients who were not eligible for anticoagulation were excluded from this study. The inclusion criteria were patients with first-time verified acute and subacute symptomatic DVT involving the femoral-popliteal, iliofemoral or iliocaval segments. The exclusion criteria included patients who were outside the 16- to 85-year age range; patients with an upper extremity thrombosis, chronic DVT, established PTS, severe renal failure or active gastrointestinal bleeding; patients cannot tolerate prone position during PMT procedure, patients who could not receive tPA or anti-coagulation therapy; terminally ill patients; and patients with contraindications to thrombolytic treatment, such as hemorrhagic stroke or other intracranial diseases, recent (<10 days) major trauma or surgery, pregnancy, recent obstetric delivery, bleeding disorder, and prolonged traumatic cardiopulmonary resuscitation.

PMT TECHNIQUE

Before PMT procedure, in selected patients, a retrievable inferior vena cava (IVC) filter was placed using either contralateral femoral or internal jugular vein access. Indications for IVC filter placement were free floating thrombus, IVC thrombus, previously documented pulmonary embolism (PE) and limited cardiopulmonary status. Using local anesthesia, a percutaneous 6F sheath was placed antegrade into either the popliteal vein under ultrasound guidance. Unfractionated heparin was administered into a peripheral vein with a target of two- to threefold activation of the partial thromboplastin time to provide anticoagulation at both the lytic site and in the systemic circulation.

Venography was performed, and the location of the thrombus was established. Then, the thrombectomy device was inserted through the introducer sheath. The tissue plasminogen activator (tPA), Al-

teplase (Actilyse, Boehringer Ingelheim, Germany) was administered through the device or introducer sheath. The vein was treated in approximately 10-cm intervals by injecting 20 ml of saline solution containing 1 mg of the tPA solution for 2 to 5 minutes; the rate depended on the patient's condition and weight and the size of the thrombus. When the device was temporarily removed, the macerated thrombus and residual lytic agent were suctioned through the sheath, and control venograms were taken to evaluate the treated segments. This procedure was repeated until the end of the thrombus was reached. Finally, the device was removed, and a completion venogram was obtained.

MEDICAL THERAPY

All of the patients either in medical therapy group, or PMT group were received subcutaneous low-molecular-weight heparin with a subsequent conversion to oral warfarin. The therapy was adjusted to attain an INR in the range of 2 to 3. All patients were encouraged to walk and to use 20-30 mmHg of thigh length compression stockings. Post-treatment duplex ultrasound imaging of the affected leg was performed at weekly intervals for 1 month and then monthly thereafter.

The study's end points were the extent of the clot lysis, major bleeding, and pulmonary emboli during the PMT and DVT evolution during the follow-up. Post-interventional venography was performed, and the venograms were graded for the quantity of the thrombus extraction compared with the venograms from before and after the treatment by the same interventionist who performed the procedure. The extent of the lysis was graded from I to III. Grade III lysis was defined as the complete resolution of the thrombus on a visual assessment of the venogram.[8] Grades II and I lysis were defined as an extent of thrombus resolution of 50-99% and <50%, respectively. Before discharge, a clinical evaluation and duplex ultrasound were performed on the treated vein segments as well as patients in medical therapy group.

COMPLICATION DEFINITIONS

According to the SIR reporting standards, major bleeding was defined as intracranial bleeding or bleeding severe enough to result in death, surgery, cessation of therapy, or a blood transfusion.[6] Minor bleeding was defined as less severe bleeding that was manageable with local compression, sheath upsizing, or dose alterations of a pharmacologic thrombolytic agent, anticoagulant, or antiplatelet drug.

FOLLOW-UP ASSESSMENTS

The efficacy outcome assessments were conducted using duplex ultrasound at the follow-up. Venous patency and the valve function were examined. Recurrent DVT and pulmonary embolisms were recorded during the follow-up. After 3 months, the symptomatic relief was assessed using the clinical symptom scale, and leg circumference. C class of the clinical, etiological, anatomical, and pathophysiological (CEAP) classification for chronic venous disease was also used for evaluation of venous disease.

ISTATISTICAL ANALYSIS

The statistical analysis was performed using IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA). The continuous data are reported as the mean ± standard deviation. The nominal data are reported as the number of subjects. Student's t-test was used to compare the mean differences between the two groups. The frequencies of the complete thrombus removal and post-thrombotic syndrome were compared using the chi-squared test. A p-value <0.05 was considered statistically significant.

RESULTS

Among the 69 patients with lower extremity DVT, the most common risk factor was chronic venous disease (Table 1). Fourty-four and twenty-five patients were managed with PMT and medical therapy, respectively. There was difference between patients in therapy groups in terms of risk factors. In entire cohort, the mean symptom duration was 6.86±4.2. Sixty-four (92.7%) patients had less than 14 days of history of DVT symptoms. There was no difference between groups in terms of demographics, site of DVT, symptom duration, difference in leg circumference and clinical symptom score (Table 2). However, patients who underwent PMT

TABLE 1: Risk factors for deep venous thrombosis in the cohort.

Risk factor	PMT (n=44)	Medical Therapy (n=25)	Total (n=69)
Chronic Venous Disease	9 (20.5%)	9 (36.0%)	18 (25.4%)
Immobization	8 (18.2%)	1 (4.0%)	9 (12.7%)
Malignancy	3 (6.8%)	4 (16.0%)	7 (9.9%)
Postpartum period	4 (9.1%)	3 (12.0%)	7 (9.9%)
Intravenous drugs	5 (11.4%)	0 (0%)	5 (7.0%)
Genetic	6 (13.6%)	1 (4%)	7 (28%)
Trauma	5 (11.4%)	0 (0%)	5 (7.0%)
Oral contraception	2 (4.5%)	2 (8.0%)	4 (5.6%)
Behcet's Disease	0 (0%)	3 (12.0%)	3 (4.2%)
Postoperative	1 (2.3%)	0 (0%)	1 (1.4%)
None	1 (2.3%)	2 (8.0%)	3 (4.2%)

TABLE 2: Patient characteristics of groups in pharmacomechanical thrombolysis (PMT) and medical therapy for symptomatic deep venous thrombosis (DVT).

	PMT (n=44)	Medical (n=25)	Total (n=69)	P
Gender (Male)	27 (61.3%)	18 (72%)	45 (65.2%)	0.412
Age (years)	46.6±17.7	51.9±14.7	48.4±16.8	0.331
Right sided thrombosis	19 (43.2%)	13 (52%)	32 (45.1%)	0.390
Bilateral thrombosis	1 (2.2%)	0	1 (1.4%)	0.422
Symptom duration (days)	7.16±4.6	6.32±3.6	6.86 ± 4.2	0.436
Acute DVT (<14 days)	41 (93.2%)	23 (92 %)	64 (92.8%)	0.837
Location of DVT				
Iliofemoral vein	28 (63.6%)	6 (24%)	34 (49.3%)	p=0.05
Common femoral vein	9 (20.4%)	0	9 (13%)	
Femoral vein	7 (15.9%)	17 (68%)	24 (24.8%)	
Popliteal vein	0	2 (8%)	2 (2.8%)	
Difference in leg circumference (cm)	4.27±1.08	3.6±0.86		p=0.05
CSS	5.39±0.7	5.24±0.6	5.3±0.7	0.417
Degree of lysis				
Complete	36 (81.8%)	0	36 (52.2%)	
50-99%	8 (18.2%)	0	8 (11.6%)	
<50%	0	25 (100%)	25 (36.2%)	
Length of hospital stay (days)	6.8±2.3	3.7±2.9		p=0.001

CSS: Clinical symptom score.

had much more proximal vein DVT than those patients taking medical therapy.

At the end of the single-session PMT procedure, lysis of more than 50% was obtained in all patients. Thirty-six patients (81.8%) had a complete thrombus (Grade III) resolution. Grades II lysis were noted in 8 (18.2%) patients. There was no recanalization any patient in medical therapy group while in the hospital. No periprocedural deaths or symptomatic pulmonary embolisms occurred. There were no systemic bleeding complications. Minor bleeding due to an access hematoma developed in one patient (2.2%).

All patients were evaluated periodically in terms of clinical symptoms and patency which was examined with Duplex scan. All patients were eval-

uated in the third month visit. Duration of clinical amelioration was shorter in PMT group than medical therapy group (3.7±1.3 vs 15.2±12.1) (p=0.001). There was amelioration in at the third month Clinical Symptom Score in comparison to the baseline measurement. However, there was significant difference between PMT and medical therapy groups at the third month Clinical Symptom Score (1.6±0.8 vs 2.1±0.9) (p=0.02). We noted diminished difference in leg circumference in both PMT and medical therapy groups (1.02±0.8 vs 1.32±0.5) but there was no statistically significant difference between groups.

Duplex ultrasound imaging at the third month visit revealed patent veins in 37 (84%) and 7 (28%) of the patients in PMT and medical therapy groups respectively (p<0.01). Duplex ultrasound imaging also showed that deep venous reflux in 5 and 1 patients with patent veins in PMT and medical therapy groups respectively. At the three month visit, the average CEAP- score was presented in Table 3. There was difference between groups in terms of CEAP-C score.

TABLE 3: C class of the clinical, etiological, anatomical, and pathophysiological (CEAP) classification of patients at the third month.

CEAP at third month	PMT (n=44)	Medical Therapy (n=25)
2	11 (25%)	1 (4%)
3	19 (43.2%)	19 (76%)
4	11 (25%)	5 (20%)
5	3 (6.8%)	0

DISCUSSION

Conventional anticoagulant treatment for acute DVT effectively prevents thrombus extension and recurrence, but does not dissolve the clot, and many patients develop post-thrombotic syndrome (PTS). Due to the suboptimal long-term results of anticoagulation therapy alone, catheter-based techniques have been employed to decrease the thrombus burden and to correct the underlying obstructions when present.[3] We aimed to examine the efficacy and safety of pharmacomechanical thrombectomy by comparing medical therapy for the treatment of DVT. The present study demonstrates the safety and efficacy of pharmacomechanical thrombectomy in the treatment of symptomatic DVT using a new rotational PMT device. Using this device, more than a 50% thrombus resolution was achieved in all patients without significant morbidity using a single-session procedure. The successful use of PMT has been described in a number of published observational DVT studies but not in any multicenter randomized trials.[3,9,10]

In our series, the treatment of lower extremity DVT with single-session rotational PMT resulted in promising primary success with minimal rates of complications. Achievement of Grade III lysis is considered the optimal result and was achieved in 81.8% of the patients. This high rate of complete lysis may be related to our patient selection. In our PMT group 93.2% of patients had acute thrombosis. The time frame from DVT onset to the initiation of PMT may play a role in successful thrombolysis. The successful thrombolysis of an acute DVT is most likely to be achieved in patients with recently formed thrombi, as evidenced by a DVT symptom duration of fewer than 10-14 days.[8] A symptom duration of greater than 10 days has been reported to result in a low rate of complete thrombolysis and in infrequent treatment failures with less than 50% thrombus removal.[11]

One of the most important early sequelae of DVT is symptoms. Patients managed with anticoagulation complains about their symptoms for a long period of time. In our PMT group, symptom relief was observed earlier than medical therapy group. There was a significant difference between PMT and medical therapy groups at the third month Clinical Symptom Score Therefore, the early elimination of venous obstruction is an important step in the symptom relief.

Bleeding is a severe complication of thrombolytic therapy. PMT offers a reasonable solution in patients with venous thromboembolisms and is associated with a lower risk of bleeding. Major bleeding is estimated to occur in 2-4% of patients receiving CDT.[2] Despite of the fact that some patients had high risk for bleeding such as postpartum, post-traumatic and post-operative, we did not

encounter any systemic bleeding complications. Minor bleeding at the access site occurred in one patient. In a retrospective study, Rao et al. demonstrated that the thrombolytic doses and infusion durations were reduced with PMT compared with conventional CDT.[9] No major bleeding complications were reported in a systematic literature review of 2528 patients with DVT treated with PMT.[12] PMT may also decrease the risk of hemorrhagic complications because of its shorter infusion intervals and lower doses of thrombolytic agents, making it a more attractive modality in high-risk post-operative patients.

Although significant proportion of patients in PMT group, had iliac vein thrombosis, we did not used iliac stents in patients with an iliofemoral venous thrombosis. Although most operators use venous stent deployment liberally during thrombolytic therapy, there is no prospective randomized trial supporting the use of iliac venous stent placements in the acute DVT. There are also conflicting data regarding the efficacy of the concomitant use of stents during thrombolysis.[8,13] In the SIR's "Reporting standards for endovascular treatment of lower extremity DVT", no specific recommendations for stent placement are given.[6]

This study has several limitations, including unmatched two groups, the small number of patients, and a limited follow-up period as well as the limited use of adjunctive balloon dilation and stent placement. This is not randomized study and type of therapy or intervention was the decision of senior author. This may be associated with a bias as well as heterogeneous distribution of cases between groups. We also did not use specific measures to evaluate patient symptoms, quality of life and post-thrombotic syndrome. However, the mean follow-up of the study is too short for evaluating a problem such as PTS, which develops over a number of years.

In summary, based on the present data, this technique may prove to be a safe and effective single-session PMT method for the treatment of acute DVT. Moreover, PMT using this device is superior to the anticoagulation.

Conflict of Interest

Authors declared no conflict of interest or financial support.

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