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Pharmaco-Mechanical Thrombectomy vs. Conventional Anticoagulant Management of Acute Lower Extremity Deep Vein Thrombosis – Long-Term Outcomes

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SOUHRN

Cíl: Cílem této studie bylo zjistit dlouhodobé výsledky farmakomechanické trombektomie a srovnat její účinnost a bezpečnost s antikoagulací v kombinaci s kompresivními punčochami u pacientů s proximální hlubokou žilní trombózou dolních končetin.
Metody: Retrospektivně byly analyzovány údaje celkem 228 pacientů, kteří se v období mezi lednem 2013 a lednem 2020 dostavili na ambulanci s akutní hlubokou žilní trombózou dolních končetin. Do skupiny s farmakomechanickou trombektomií a následnou antikoagulací (skupina 1) bylo zařazeno 112 pacientů, přičemž ve skupině s klasickou antikoagulací v kombinaci s použitím kompresivních punčoch (skupina 2) bylo 116 pacientů.
Výsledky: Po šestiměsíčním sledování nebyl ve výskytu posttrombotického syndromu hodnoceného skórovacím systémem Villalta Scores zaznamenán statisticky významný rozdíl. Po 12, 24 a 36 měsících sledování však byla incidence posttrombotického syndromu ve skupině 1 nižší než ve skupině 2 (21,4 %; resp. 30,3 % a 36,6 % vs. 33,6 %, resp. 53,4 % a 61,2 %). Po 36 měsících byla rekanalizace nedostatečná u 41 ze 112 pacientů ve skupině 1 a u 71 ze 116 pacientů ve skupině 2, což odpovídalo snížení absolutního rizika o 25,6 % (95% CI 9,2–37,5 %; p = 0,001). Mezi 6. až 36. měsícem sledování došlo k recidivě trombózy statisticky významně častěji ve skupině 2 než ve skupině 1 (18,9 % vs. 7,1 %; p = 0,002).
Závěr: Výsledky naší studie prokázaly, že farmakomechanická trombektomie představuje bezpečný a účinný způsob léčby akutní hluboké žilní trombózy dolních končetin. Ve srovnání s antikoagulací v kombinaci s použitím kompresivních punčoch byla farmakomechanická trombektomie v dlouhodobém sledování spojena s nižší incidencí posttrombotického syndromu a nižší recidivou žilní trombózy.

Keywords:
Anticoagulant therapy
Deep vein thrombosis (DVT)
Pharmaco-mechanical therapy (PMT)
Post-thrombotic syndrome (PTS)

ABSTRACT

Objective: In this study, we aimed to evaluate the long-term effects of pharmaco-mechanical thrombectomy and compare its efficiency and safety against anticoagulation together with the use of compression stockings in patients with proximal deep vein thrombosis of the lower extremity.
Methods: A total of 228 patients, between January 2013 and January 2020, who presented to the clinic with acute deep vein thrombosis of the lower extremity were investigated retrospectively. There were 112 patients in the anticoagulation following pharmacomechanical thrombectomy group (Group 1) and 116 patients in the conventional anticoagulation with compression stockings group (Group 2).
Results: There was no significant difference in the post-thrombotic syndrome occurrence assessed with Villalta Scores at 6-month follow-up. However; at 12-, 24- and 36-month follow-up, the incidence of the post-thrombotic syndrome was lower in the Group 1 compared to Group 2 (21.4%, 30.3%, 36.6% vs. 33.6%, 53.4%, 61.2%). Insufficient recanalization was present in 41 of 112 patients at 36 months in the Group 1, and in 71 of 116 patients in Group 2 at 36 months; correlating to an absolute risk reduction of 25.6% (95% CI 9.2–37.5; p = 0.001). The recurrent thrombosis rates in the Group 2 were significantly higher than Group 1 (18.9% vs 7.1%; p = 0.002) in the 6- to 36-month follow-up.
Conclusion: The results of our study demonstrated that pharmacomechanical thrombectomy is a safe and effective treatment modality in case of lower extremity acute deep vein thrombosis. It has been associated with reduced post-thrombotic syndrome and recurrent venous thrombosis rates in the long-term follow-up when compared with the anticoagulation and compression stockings.

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Introduction

Deep vein thrombosis (DVT) is an important reason of mortality and morbidity in human life. Thromboembolism is associated with life and limb threatening complications such as pulmonary embolism, plegmasia cerulea dolens and plegmasia alba dolens.[1] It may also result in a clinical scenario with heavily disturbing effects on the patients' quality of life, known as post-thrombotic syndrome (PTS).[1] Post-thrombotic syndrome is a condition of chronic deep venous insufficiency, and it is characterized with extremity pain, swelling, venous claudication and skin ulcerations.[1,2] Post-thrombotic syndrome is seen in at least one-third of the patients with acute DVT.[3] It is costly for the health care system and associated with significant disability for the patients.

The conventional treatment of DVT consists of anticoagulation therapies; including low-molecular weight heparin, unfractionated heparin or fondaparinux bridging followed by oral vitamin K antagonists for at least 3–6 months. New generation oral anticoagulants: dabigatran, rivaroxaban, apixaban, and edoxaban are becoming more popular choice of anticoagulation with promising safety and efficiency studies in case of acute DVT since they do not require repeated blood analysis, and therefore provide easier and safer patient compliance and follow up. Even though, anticoagulation is effective in terms of prevention of pulmonary emboli (PE) and thrombus extension, their effect on the clot lysis is minimal regardless of the type of anticoagulation.[4] As a result; anticoagulation alone, or with compression stockings may have limited effect on the venous obstruction, venous scarring and PTS formation following acute DVT.[5–8] Therefore, the "open vein concept", meaning early restoration of the venous patency and venous valvular preservation, has been endorsed in the late studies.[7,9]

Interventional approaches to sustain an "open vein" could potentially reduce the treatment time and decrease overall health care costs related to the formation of PTS. Since PTS is associated with the proximal venous obstructions, these interventional techniques provide the greatest benefits for patients with acute presentation of extensive proximal DVT, decreasing the risk of PTS formation and/or the severity of PTS if they ever occur.[4,10] In addition, they play an important role in cases with acute limb threatening conditions due to venous occlusions or severe DVT symptoms.

The pharmacomechanical thrombectomy (PMT) is a combinatory approach which consists of mechanical breakdown of the blood clot and catheter directed thrombolysis, aiming to restore early venous patency. Although adverse outcomes are rare in interventional approaches against DVT, a potential devastating outcome is intracranial bleeding. The objective of the PMT combination is to enlarge the surface area of the thrombus by mechanical clot disintegration, and to increase the effectivity of fibrinolytic infusion even in low doses; thereby minimizing the risk of bleeding while effectively reducing the risk of PTS.[11–14]

In the current research we aimed to evaluate the safety and the effectivity of PMT and compare the results with conventional DVT treatment with anticoagulant therapy combined with compression stockings.

Patients and methods

The cohort included 228 patients who presented to the clinic with the symptoms of acute (<14 days) proximal deep-vein thrombosis between January 2013 and January 2020. Patients were investigated retrospectively. Patients were divided into two groups as receiving anticoagulation therapy together with pharmacomechanical thrombectomy (PMT) (Group 1, APMT group) and anticoagulation therapy with compression stockings (Group 2, ACS group) on admission. As the clinical experience in PMT increased, it became the more frequently preferred choice of treatment in latter cases when compared with the initial higher number of patients scheduled for conventional DVT treatment.

The primary goal of the study was to assess the safety and effectivity of the PMT by comparing the occurrence rate and the severity of post-thrombotic syndrome (PTS) among two groups, between 6 and 36 months of follow-up time, as well as estimating the major bleeding incidences and overall mortality. Ethical approval was not required due to the retrospective nature of the study.

Only proximally located acute DVT cases were enrolled in the study including: the common femoral vein, iliac vein or inferior caval vein (with or without other involved ipsilateral veins). Venous duplex ultrasonography (USG) was used for the diagnosis in all patients. The exclusion criteria were: being younger than 16 years or older than 75 years, pregnancy, symptoms persisting for more than 28 days, high bleeding risk, life-expectancy below 6 months due to active cancer, already existing post-thrombotic syndrome, or previous ipsilateral deep-vein thrombosis in the last 2 years.

Both groups received initial and long-term oral anticoagulation therapy which continued for at least six months. Subcutaneous low molecular weight heparin was administered to all patients in the ambulatory phase, then resumed with oral warfarin; aiming the international normalized ratio (INR) to be in the range between 2–3. In both groups above the knee, class II (30–40 mmHg pressure) compression stockings were prescribed and renewed in every 6 months. The patients who are treated with new generation anticoagulants are not included in the study. The anticoagulation treatment regimen was oral warfarin together with 100 mg acetylsalicylic acid.

In the APMT group, Cleaner thrombectomy device (Rex Medical, Fort Worth, US and Argon Medical Devices, Inc, Plano, US) was utilized. PMT device consists of an "S" shaped tip, rotating at a speed of 4,000 rpm. While gently disintegrating the blood clot, distal ports of the device located at the helical tip allow simultaneous tPA (tissue plasminogen activator) infusion directly into the fragmentated thrombus.

Pharmacomechanical thrombectomy technique

The technique of PMT was described previously.[10] A retrievable inferior vena cava (IVC) filter (option retrievable vena cava filter; Argon Medical Devices, Plano, Texas, US) was inserted through contralateral femoral or internal jugular vein access before the procedure in all patients. All of the procedures were performed with local anesthesia. A percutaneous 6-F sheath was placed into the popliteal

or posterior tibial vein under the ultrasonography. Unfractionated heparin (100 units/kg) was administered. The activation of the partial thromboplastin time was raised two- to threefold and activated clotting time reached 180–220 seconds. A 6-F Cleaner thrombectomy device was inserted via the introducer sheath. A recombinant form of tPA (alteplase; Actilyse; Boehringer Ingelheim, Ingelheim am Rhein, Germany) was administered via the port side of the device. S-shaped wire was initiated firstly. Thrombolysis was applied for 2–5 minutes, then the device was turned off and withdrawn temporarily. The macerated thrombus and lytic particles were aspirated via the sheath. Following the step, venogram was performed to assess the treated area and the device was applied for repeated thrombolysis to the more proximal segments. The rate of the procedure was adjusted according to the patient's weight and the thrombus. Following the removal of the device, the last control venogram was performed. There was no hesitation about reintervention in the case that the thrombus removal was less than 50% of the thrombosed segment. CDT was considered only for patients with residual thrombosis following PMT as a complementary procedure. In these patients, if a residual thrombosis was revealed by the control venogram, 1 mg/h tPA was administered by a 4-F infusion catheter (Cragg McNamara valved infusion catheter; ev3, Irvine, California) for 24 hours. Percutaneous transluminal angioplasty was performed in the presence of an advanced stenosis or non-responding iliocaval obstructions. Self-expanding stents were only considered for chronic cases and were performed in the follow-up as reinterventions. Large (16–18 mm in diameter) stents (Boston Scientific, Natick, Massachusetts) were applied with 1–2 cm distance of stent joints in these cases.[10]

Periprocedural IVC filters are not necessarily used in PMT; however, retrievable filters are effective in preventing pulmonary embolism by capturing the thrombus. In our study, we did not observe severe complications associated with IVC filter and hence, our practice evolved to place temporary filters routinely.

After discharge from the hospital, follow-up visits were organized at the 1st, 3rd, 6th, 12th, 24th, and 36th months. Duplex ultrasonography examination was performed in each visit to evaluate the venous patency. Control venograms were performed at the 12th, 24th, and 36th months and patients were graded according to the thrombus extraction compared with their initial venography. Accordingly, Grade I lysis was defined as the thrombus resolution less than 50%, Grade II lysis was defined as 50–99% resolution and Grade III lysis was the complete (100%) thrombus resolution.

Patients in both groups were followed up in terms of thrombolysis, bleeding, occurrence of pulmonary emboli and DVT. From the 3rd month follow-up, the PTS was assessed per the Villalta scale:[15] including five symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and six objective signs (edema, skin induration, hyperpigmentation, venous ectasia, redness, and pain during calf compression). Each symptom or sign was rated as 0 (absent), 1 (mild), 2 (moderate), or 3 (severe). The points were then added to determine the total score. Scores of less than 5 indicated the absence of PTS, scores of 5–9 indicated mild PTS, scores of 10–14 indicated moderate PTS, and scores greater than 15 or ulceration indicated severe PTS.[15]

Statistical analysis

All the statistical analyses were performed with SPSS 23.0 (IBM, Armonk, New York, US). Data are expressed as mean ± SD for continuous variables and as counts and percentages for categorical variables. Comparisons of clinical, angiographic, and procedural characteristics were performed with the Fisher exact test for categorical variables and Mann-Whitney U test for continuous variables. Odds ratio (OR) and 95% confidence interval (CI) were calculated with univariate logistic regression. Variables with a p value ≤ 0.2 in the univariate model or known to be significantly associated were entered into a multivariate logistic regression model. The target vessel revascularization, primary and secondary patency rates during the follow-up were presented with Kaplan-Meier event-free survival curves. A value of $p < 0.05$ was described statistically significant.

Results

A total of 228 patients, 112 (64 men, 48 women) in APMT group and 116 (67 men, 49 women) in ACS group were retrieved from the computer database systems of the hospitals. Mean age was 51.12±7.43 (range: 19–75) years. The mean duration of symptoms was 9.2±1.4 days in APMT groups and 8.7±0.6 days in the ACS group (range: 1–28 days). The mean amount of tPA use was 22.8±10.4 mg (range: 12–45) in the APMT group. The lesions were on the left side in 54.5% (61/112) patients in the APMT group, and 56% (65/116) left side in the ACS group. All patients were followed from 30 days to 36 months after the treatment.

Demographic characteristics and risk factors for venous thrombosis did not differ between the groups. Ninety two patients (82.1%) in the APMT group and 102 patients (87.9%) in the ACS group had 1–7 days of symptoms, while the rest had 8–14 days of symptoms. Phlegmasia cerulea dolens was present in 6 patients (5.6%) in the APMT group; and 3 patients (2.6%) in the ACS group (Table 1). Iliofemoropopliteal thrombosis was noted in 62 patients (55.3%) in the APMT group; and in 67 patients (57.5%) in the ACS group (Table 2).

One hundred and four of the 112 patients were treated in a single session, and eight (7.1%) patients with residual thrombus required supplementary 24 hours catheter directed lytic infusion. All the procedures were completed with a 100% success rate and there were no complications regarding the PMT device. Prompt clinical improvement was observed in 107 patients (95.5%) in APMT group and in 52 (44.8%) patients in the ACS group. Limb salvage was attained in all nine patients from both groups, who were initially presented with phlegmasia cerulea dolens; however, the three patients who were from ACS group had longer hospital stay and a limited mobility. Two of the patients with non-responding chronic occlusions (1.7%) in the APMT group required additional stenting with self-expanding stents (Wall stent, Boston Scientific Inc., Galway, Ireland), performed in the follow-up as reintervention. No periprocedural deaths, symptomatic pulmonary

Table 1 – Demographic characteristics and risk factors of patients

Variables	PMT (n = 112)	ACST (n = 116)	*p*-value
Age (years)	58.4±25.5	57.6±26.2	0.569
Sex (male/female)	64/48	67/49	0.628
Duration of symptoms (days – mean)	9.2	8.7	0.425
DVT affected limbs			1.000
Left side	54.5% (61/112)	56% (65/116)	0.782
Right side	41.9% (47/112)	40.5% (47/116)	0.496
Bilateral	3.5% (4/112)	3.4% (4/116)	0.588
Acute DVT (1–7 days)	82.1% (92/112)	87.9% (102/116)	0.453
Acute DVT (8–14 days)	17.9% (20/112)	12.1% (14/116)	0.658
Phlegmasia cerulea dolens	5.4% (6/112)	2.6% (3/116)	0.156
Diabetes mellitus	14.2% (16/112)	12.9% (15/116)	0.589
Hypertension	8.9% (10/112)	7.8% (9/116)	0.635
Dislipidemia	9.8% (11/112)	10.3% (12/116)	0.854
Smoking	43.7% (49/112)	44.8% (52/116)	0.423
CAD	11.6% (13/112)	10.3% (12/116)	0.245
COPD	12.5% (14/112)	13.7% (16/116)	0.426
CHF	5.3% (6/112)	6% (7/116)	0.238
CRD	3.5% (4/112)	2.5% (3/116)	0.263
Symptoms			1.000
Limb swelling	96.4% (108/112)	90.5% (105/116)	0.362
Palpitation	25.8% (29/112)	26.7% (31/116)	0.586
Cramps	33.9% (38/112)	37% (43/116)	0.475
Heaviness	86.6% (97/112)	87.9% (102/116)	0.562
Leg pain	73.2% (82/112)	76.7% (89/116)	0.385
Venous ectasia	24.1% (27/112)	25.1% (29/116)	0.457
Transient risk factors for VTE			1.000
Trauma, previous 3 months	12.5% (14/112)	14.6% (17/116)	0.576
Orthopedic surgery, previous 3 months	10.7% (12/112)	12% (14/116)	0.459
Brain surgery, previous 3 months	3.5% (4/112)	4.3% (5/116)	0.586
Gynecologic surgery, previous 3 months	5.3% (5/112)	5.1% (6/116)	0.754
General surgery, previous 3 months	2.6% (3/112)	3.5% (4/116)	0.596
Short-term immobility	20.5% (23/112)	23.2% (27/116)	0.487
Infection, previous 3 months	1.7% (2/112)	2.5% (3/116)	0.569
Pregnancy, previous 3 months	4.4% (5/112)	5.1% (6/116)	0.788
Oral contraceptive use	3.5% (4/112)	4.3% (5/116)	0.985
Hormone replacement therapy	1.7% (2/112)	2.5% (3/116)	0.689
Permanent risk factors for VTE			1.000
Previous venous thrombosis	2.7% (3/112)	3.4% (4/116)	0.523
Cancer	10.7% (12/112)	12% (14/116)	0.649
Obesity	4.4% (5/112)	6% (7/116)	0.854
Behçet disease	7.1% (8/112)	8.6% (10/116)	0.682
Inflammatory bowel disease	1.7% (2/112)	1.7% (2/116)	0.546
Venous insufficiency (CEAP 0–4) diagnosed before VTE	11.6% (13/112)	12.9% (15/116)	0.422
First-degree relative venous disease	13.3%(15/112)	16.4%(19/116)	0.526
Genetic factors carrying for thrombophilia			1.000

Pokračování na další straně

Table 1 – Demographic characteristics and risk factors of patients			
Variables	**PMT (n = 112)**	**ACST (n = 116)**	***p*-value**
Factor V Leiden mutation			
Heterozygous F5 rs6025 polymorphism	23.2% (26/112)	21.5% (25/116)	0.256
Homozygous F5 rs6025 polymorphism	2.6% (3/112)	1.7% (2/116)	0.235
Protein C deficiency	20.5% (23/112)	22.4% (26/116)	0.563
Protein S deficiency	16.9% (19/112)	18.1% (21/116)	0.526
Lupus anticoagulant	4.4% (5/112)	2.5% (3/116)	0.496
Combined thrombophilia	14.2% (16/112)	15.5% (18/116)	0.624
No specific cause	1.7% (2/112)	1.7% (2/116)	0.322

ACST – anticoagulation-stocking treatment; CAD – coronary artery disease; COPD – chronic obstructive pulmonary disease; CRD – chronic renal disease; DVT – deep venous thrombosis; CHF – chronic heart failure; PMT – pharmacomechanical thrombectomy; VTE – venous thromboembolism.

Table 2 – Thrombi locations in lower extremity veins			
Thrombosed veins	**PMT (n = 112)**	**ACST (n = 116)**	***p*-value**
IVC/CIV/CFV	0.9% (1/112)	0.9% (1/116)	0.896
IVC/CIV/CFV/external veins	1.8% (2/112)	1.7% (2/116)	0.659
CIV/CFV	16.1% (18/112)	14.6% (17/116)	0.789
IVC/CFV/CIV	1.8% (2/112)	2.6% (3/116)	0.568
CFV/SFV	19.6%(22/112)	18.9% (22/116)	0.695
IVC/CIV/CFV/SFV/PV	4.5% (5/112)	3.4% (4/116)	0.579
CIV/CFV/SFV/PV	55.3% (62/112)	57.7% (67/116)	0.478

ACST – anticoagulation-stocking treatment; CFV – common femoral vein; CIV – common iliac vein; IVC – inferior vena cava; PMT – pharmacomechanical thrombectomy; PV – popliteal vein; SFV – superficial femoral vein.

Table 3 – PTS rates after treatment (short-term and long-term outcomes)			
PTS rates	**PMT (n = 112)**	**ACST (n = 116)**	***p*-value**
30 day	3.5% (4/112)	9.4% (11/116)	0.763
6 months	11.6% (13/112)	19.8% (23/116)	0.058
12 months	21.4% (24/112)	33.6% (39/116)	**0.027**
24 months	30.3% (34/112)	53.4% (62/116)	**0.002**
36 months	36.6% (41/112)	61.2% (71/116)	**0.001**

ACST – anticoagulation-stocking treatment; PMT – pharmacomechanical thrombectomy; PTS – post-thrombotic syndrome. Post-thrombotic syndrome (PTS) defined as Villalta score of 5 points or higher.

embolisms or major bleeding occurred in both groups during hospital stay.

There were no significant differences in the post-thrombotic syndrome (PTS) occurrence assessed with Villalta Scores at 6-month follow-up. However; at 12-, 24- and 36-month follow-up, the incidence of the PTS was lower in the APMT group when compared with the ACS group (21.4%, 30.3%, 36.6% vs 33.6%, 53.4%, 61.2%). Insufficient recanalization was present in 41 of 112 patients at 36 months in the APMT group, and in 71 of 116 patients in ACS group at 36 months; correlating to an absolute risk reduction of 25.6% (95% CI 9.2–37.5; $p = 0.001$) (Table 3). There was no statistical correlation between the duration of symptoms on admission and development of PTS measured with Villalta Scores.

The effectiveness of the treatment for both groups was evaluated according to the following criteria: thrombus clearance of 100% was defined as Grade III, 50–99% as Grade II, and <50% as Grade I thrombus removal. Complete recanalization (Grade III) (Fig. 1) was achieved in 92.8% (104/112) of the APMT group, and in 44.8% (52/116) of the ACS group. Near-complete recanalization (Grade II) was achieved in 5.3% (6/112) of the APMT group, and in 14.4% (17/116) of the ACS group. Partial Grade I recanalization was present in 1.9% (2/112) of the PMT group, and in 22.4% (26/116) of the ACS group. Two patients in the APMT group with Grade I recanalization were observed to have non-responding chronic occlusion segments and later scheduled for stent implantation. In 18.1% (21/116) of the ACS group no recanalization at all

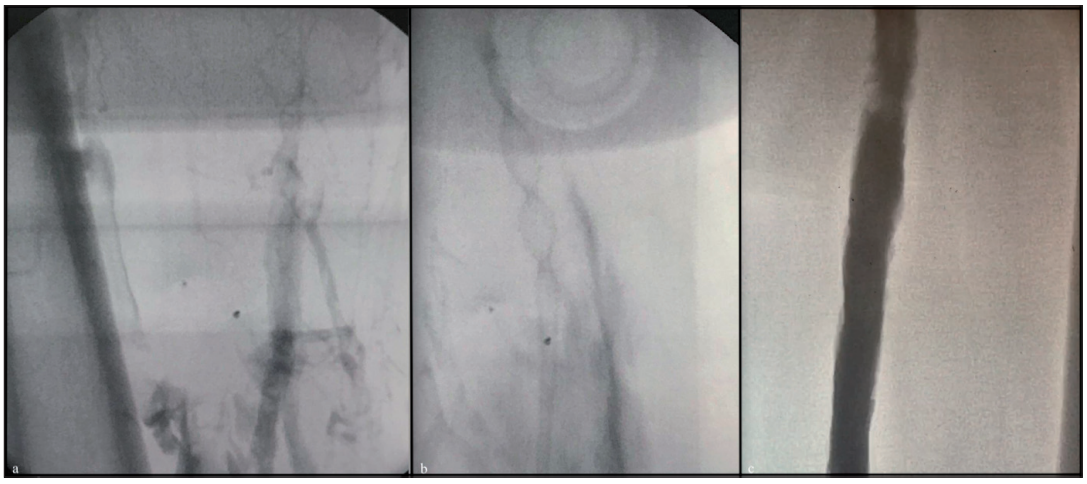

Fig. 1 – Deep vein thrombosis of the common femoral vein treated with pharmacomechanical thrombectomy revealing complete resolution and recanalization.

Table 4 – Recanalization rates after treatments by duplex ultrasonography (short- and long-term outcomes)

Recanalization by DUS	PMT (n = 112)	ACST (n = 116)	*p*-value
30 day			
Grade III (complete)	92.8% (104/112)	44.8% (52/116)	0.023
Grade II (near-complete)	5.3% (6/112)	14.4% (17/116)	0.012
Grade I (partial)	1.9% (2/112)	22.4% (26/116)	0.001
None	0	18.1% (21/116)	<0.001
6 months			
Grade III (complete)	90.1% (101/112)	40.5% (47/116)	<0.001
Grade II (near-complete)	7.1% (8/112)	16.3% (19/116)	0.021
Grade I (partial)	2.6% (3/112)	25% (29/116)	0.003
None	0	18.1% (21/116)	<0.001
12 months			
Grade III (complete)	89.2% (100/112)	37.9% (44/116)	<0.001
Grade II (near-complete)	8% (9/112)	18.1% (21/116)	0.032
Grade I (partial)	2.6% (3/112)	26.6% (30/116)	0.002
None	0	18.1% (21/116)	<0.001

ACST – anticoagulation-stocking treatment; DUS – doppler ultrasonography; PMT – pharmacomechanical thrombectomy.

was detected. Grade 3 recanalization rates by duplex USG scan were significantly higher in the APMT group. (89.2% CI 95% 68.2-110.7; 40.5% CI 95% 24.6-56.1; p<0.001) (Table 4). Moreover, Grade III recanalization rates via venography imaging were higher in the PMT group at 24 and 36 months (84.8%; CI 95% 58.5–110.7; 34.4 95% CI 21.2–47.3; 82.1 CI 95% 55.3–108.4; 31.8 CI 95% 19.7–44.5; p <0.001) (Table 5).

The recurrent thrombosis rates in the ACS group were significantly higher than APMT group (18.9% vs 7.1%; p = 0.002) from 6 months to 36 months of follow-up period (Table 6). Major bleeding was defined as intracranial bleeding or severe bleeding resulting in death, surgery, cessation of therapy or blood transfusion, and occurred in 1 patient (0.89%) in APMT group, and in 2 patients (1.7%) in ACS group (p = 0.242) (Table 7) during 36 months of follow-up. The major bleeding events in ACS group consist of an abdominal wall hematoma requiring massive blood transfusion and resulting in surgery in one patient, and cerebral hemorrhage in another one. The patient with major bleeding in APMT group had spinal cord hemorrhage necessitating massive blood transfusion and eventually needed surgery. Hemoglobinuria, classified as minor bleeding, was noted in seven patients in APMT group and in 5 patients in ACT group, which resolved spontaneously within 24 hours. There was no significantly difference for minor bleeding events (p = 0.568) between the two groups (Table 7). All-cause mortality rates, including pulmonary embolism and systemic major bleeding, were not statistically different between the two groups at the follow-up period (Table 8) (p >0.05).

Table 5 – Recanalization rates via venography (long-term outcomes)			
	PMT (n = 112)	ACST (n = 116)	*p*-value
12 months			
Grade III (complete)	89.2% (100/112)	37.9% (44/116)	<0.001
Grade II (near-complete)	8% (9/112)	18.1% (21/116)	0.032
Grade I (partial)	2.6% (3/112)	26.6% (30/116)	0.002
None	0	18.1% (21/116)	<0.001
24 months			
Grade III (complete)	84.8% (95/112)	34.4% (40/116)	<0.001
Grade II (near-complete)	11.6% (13/112)	19.8% (23/116)	0.003
Grade I (partial)	3.6% (4/112)	26.7% (31/116)	<0.001
None	0	18.1% (21/116)	<0.001
36 months			
Grade III (complete)	82.1% (92/112)	31.8% (37/116)	<0.001
Grade II (near-complete)	13.3% (15/112)	20.6% (24/116)	0.026
Grade I (partial)	4.4% (5/112)	28.4% (33/116)	0.001
None	0	18.1% (21/116)	<0.001

ACST – anticoagulation-stocking treatment; PMT – pharmacomechanical thrombectomy.

Table 6 – Recurrence of DVT			
Recurrence seen veins	**PMT (n = 112)**	**ACST (n = 116)**	***p*-value**
30 day	0	1.8% (3/116)	0.228
IVC	0	1.7% (1/116)	0.256
CFV	0	1.7% (1/116)	0.368
SFV/PV	0	1.7% (1/116)	0.569
6 months	0.89% (1/112)	5.1% (6/116)	0.024
CFV	0.89% (1/112)	0	0.569
SFV	0	0.89% (1/116)	0.128
SFV/PV	0	1.7% (2/116)	0.246
12 months	2.6% (3/112)	11.2% (13/116)	<0.001
CFV	0	1.7% (2/116)	0.068
SFV	0	2.5% (3/116)	0.055
SFV/PV	0.89% (1/112)	0.86% (1/116)	0.256
PV	0.89% (1/112)	0.86% (1/116)	0.452
24 months	4.4% (5/112)	15.5% (18/116)	0.002
CIV/external veins	0.89% (1/112)	0	0.565
CFV/SFV	0	1.7% (2/116)	0.238
SFV	0	1.7% (2/116)	0.423
SFV/PV	0.89% (1/112)	0.86% (1/116)	0.538
36 months	7.1% (8/112)	18.9% (22/116)	0.002
IVC/CIV/external veins	0.89% (1/112)	0.86% (1/116)	0.562
CFV	0.89% (1/112)	0	0.543
CFV/SFV	0.89% (1/112)	0.86% (1/116)	0.457
SFV/PV	0.89% (1/112)	1.7% (2/116)	0.569

ACST – anticoagulation-stocking treatment; CFV – common femoral vein; CIV – common iliac vein; DVT – deep venous thrombosis; IVC – inferior vena cava; PMT – pharmacomechanical thrombectomy; PV – popliteal vein; SFV – superficial femoral vein.

Table 7 – Risk of occurrence of PE and major–minor bleeding

	PMT	ACST	*p*-value
Major PE	0.89% (1/112)	4.4% (5/116)	0.238
30 days	0	0.86% (1/116)	0.128
6 months	0	1.7% (2/116)	0.324
12 months	0.89% (1/112)	2.6% (3/116)	0.458
24 months	0.89% (1/112)	3.5% (4/116)	0.269
36 months	0.89% (1/112)	4.4% (5/116)	0.238
Minor PE	2.6% (3/112)	5.5% (6/116)	0.342
30 days	0	0.86% (1/116)	0.247
6 months	0.89% (1/112)	1.7% (2/116)	0.156
12 months	0.89% (1/112)	3.5% (4/116)	0.234
24 months	1.7% (2/112)	5.5% (6/116)	0.225
36 months	2.6% (3/112)	5.5% (6/116)	0.342
Major bleeding	0.89% (1/112)	1.7% (2/116)	0.242
After op-30 days	0	0.86% (1/116)	0.324
6 months	0	0.86% (1/116)	0.249
12 months	0	1.7% (2/116)	0.421
24 months	0.89% (1/112)	1.7% (2/116)	0.238
36 months	0.89% (1/112)	1.7% (2/116)	0.242
Minor bleeding	4.4% (5/112)	6.5% (7/116)	0.568
After op-30 days	1.7% (2/112)	2.6% (3/116)	0.263
6 months	2.7% (3/112)	3.5% (4/116)	0.396
12 months	3.6% (4/112)	5.5% (6/116)	0.437
24 months	3.6% (4/112)	6.5% (7/116)	0.359
36 months	4.4% (5/112)	6.5% (7/116)	0.285

ACST – anticoagulation-stocking treatment; PE – pulmonary embolism; PMT – pharmacomechanical thrombectomy.

Table 8 – All-cause mortality rates

	PMT (n = 112)	ACST (n = 116)	*p*-value
30 days			
Major PE	0	0.86% (1/116)	0.269
Major bleeding	0	0.86% (1/116)	0.257
Other	0	0	0
6 months			
Major PE	0	0.86% (1/116)	0.526
Major bleeding	0	0.86% (1/116)	0.257
Other	0	0	0
12 months			
Major PE	0.89% (1/112)	0.86% (1/116)	0.574
Major bleeding	0	1.7% (2/116)	0.257
Other	0	0	0
24 months			
Major PE	0	0.86% (1/116)	0.523
Major bleeding	0.89% (1/112)	1.7% (2/116)	0.896
Other	0	**0**	0
36 months			
Major PE	0	0.86% (1/116)	0.375
Major bleeding	0	1.7% (2/116)	0.522
Other	0.89% (1/112)	0	0.968

ACST – anticoagulation-compression stocking treatment; PE – pulmonary embolism; PMT – pharmacomechanical thrombectomy.

At 36-month follow-up; the use of maintenance drugs (aspirin, venotonic drugs, or warfarin) and compression stocking use (Class II or over) were more frequent in the ACS group compared to APMT group (p <0.05). In addition, venous operational procedures intended to relieve PTS symptoms (open surgery, laser or RF ablation, vein closure systems for insufficient greater or lesser saphenous veins or the perforator veins) were significantly higher in the ACT group (p <0.001). Moreover, wound care techniques for venous ulcers (intralesional or topical epidermal growth factor applications, stem cell injections, platelet rich plasma applications, or local wound debridement) were required and applied more often in the ACS group compared to APMT group (p <0.001). Finally, loss of labor and dismissal rates due to venous thrombotic events were higher in the ACS group than the APMT group in the long-term (p <0.05).

Discussion

The conventional treatment of the DVT is anticoagulation, prescribed for 3–6 months. The main aim of this treatment is to prevent pulmonary embolism, which is the most serious and life-threatening complication of thromboembolism. Oral anticoagulation also prevents thromboembolism progression, but it is ineffective in clot lysis;[4] therefore, the treatment alone with anticoagulation is not enough to preserve venous patency, leaving patients with devastating symptoms of PTS.[5–8] Post-thrombotic syndrome is seen in 35–70% of the patients.[16,17]

In the pathophysiology of the PTS; the residual thrombus initiates an inflammatory mechanism which results in valvular scarring; promoting venous reflux and causing venous hypertension.[18] Moreover, the risk of PTS is higher in the cases where proximal DVT is present, especially involving iliac or common femoral veins.[17] Therefore, effective clot lysis is crucial to avoid this scenario in proximally located DVTs. In our study, we only included the patients who had DVT for the first time, involving the iliofemoral or iliocaval segments, and compared the effects of PMT with anticoagulation with compression therapy on venous recanalization and development of PTS. Complete and near complete recanalization was targeted, and Grade III clot lysis, examined by venography, was achieved in 89.2%, 84.8% and 81.1% the PMT group at 12, 24 and 36 months respectively; whereas these ratios only remained at 37.9%, 34.4% and 31.8% in the ACS group.

Comparing with the new onset DVT, patients are at higher risk of having recurrent DVT even after receiving anticoagulation therapy.[19] The role of residual thrombus in DVT recurrence is emphasized in the literature,[20,21] as

the clot reformation most likely originates from the remnants of previous thrombi. Accordingly, in the cases where effective thrombus clearance is sustained, decreased number of recurrent DVTs should be expected. Among our APMT and ACS treatment groups, significant differences in venous recanalization appeared inversely correlated with the recurrent DVT rates at the first year follow up, as expected. In the APMT group the recurrence DVT rate was 2.6%, and was significantly decreased compared to 11.2% DVT recurrence rate in the ACT group at 12 months.

The success of venous recanalization is also affected by the age of the thrombus. Recently formed thrombi result in better technical success in terms of thrombus clearance,[22] and early thrombus removal is advised in the acute phase of iliofemoral DVT, when symptoms are persisting less than 14 days.[23] On the other hand, it is demonstrated that the patients with DVT having symptoms lasting longer than 10 days had lower complete thrombolysis rates with catheter directed thrombolysis.[24] In our study, we subcategorized the acute DVT patients into 0–7 days and 8–14 days groups in order to investigate the role of symptom duration in the development of the PTS. There was no statistical correlation between the duration of symptoms on admission in the acute phase, and the development of PTS measured by Villalta Score.

Compression stockings have been conventionally prescribed following acute DVT, aiming to prevent PTS and recurrent DVT, and to increase the patients' quality of live. It has also been recommended by the 2012 CHEST guidelines.[25] Nevertheless, the evidence of these recommendations was limited and required a more extended investigation. In late 2014, a randomized prospective SOX trial revealed that the use of compression stockings for two years following DVT was unnecessary and ineffective in terms of PTS prevention.[26] To the best of our current knowledge, compression stockings are likely to have minimal importance on the routine use against PTS; however, patients with already existing PTS and symptomatically edematous patients with significant venous congestion could benefit from them.[5] In our study, the data collection dates back to the beginning of 2013, when "no compression stockings" approach had not been clinically adopted at that time, and therefore compression stockings were routinely prescribed and continued in acute DVT patients in combination therapy with anticoagulation.

The major setback for the early clot removal techniques to become gold standard in treating DVTs is that recent multi-centered randomized controlled trials were insufficient to demonstrate their efficiency in the prevention of PTS. In ATTRACT trial, both iliofemoral and femoropopliteal lesions were included and the results showed no difference between PMT and anticoagulation groups in terms of PTS occurrence; although, subgroup analysis demonstrated decreased number of moderate to severe PTS in patients who initially had iliofemoral DVTs and underwent PMT.[27] CAVENT trial also demonstrated reduced but statistically insignificant rates of PTS after catheter directed thrombolysis when compared with the standard therapy.[28] However, the likelihood of bleeding events was found to be higher following catheter directed thrombolysis and anticoagulation.[28] The CAVA trial, compared catheter directed thrombolysis with anticoagulation alone for proximal DVT and also did not show statistical significance in PTS occurrence in one year.[29] Post-thrombotic syndrome rates were 29% and 35% in the intervention and standard therapy groups, respectively, but only the half of the patients were considered to be treated successfully with effective thrombolysis and adequate stenting.[29]

We included only proximally located acute illiofemoral DVTs, followed the patients for three years and compared the results of APMT and ACT therapies. Total recanalization (Grade III), in terms of technical success, was achieved in 92.8% of the patients, and PTS rates were significantly lower in APMT group in 24 and 36 months. In addition, there was no significant difference in the likelihood of major and minor bleeding incidences, in contrast to catheter directed thrombolysis therapies. Decreased dose requirements of tPA for effective recanalization in pharmacomechanical thrombectomy cases could be responsible for lower bleeding rates, as previously mentioned in the literature.[30,31]

Conclusion

Methodological flaws in the trials such as incorrect patient selection criteria, unsatisfactory technical success and inadequate stenting rates are accounted for the underpowering results of early clot removal. Nevertheless, the inconsistency between the published data and the large-scale experience belonging to the clinical communities warrant further investigation on the open vein concept. Our study demonstrated that PMT is a safe and effective method of venous recanalization compared to anticoagulation with compression stockings, with reduced PTS and VTE reoccurrence rates in the long-term follow-up. Together with the technological advances offering wide range of PMT options, the relationship between the technical success of early venous recanalization and their long-term clinical outcome reported by the selected centers of excellence remains to be intriguing, and could be determinative for the future of iliofemoral DVT treatment.

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