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International Angiology 2018 October;37(5):400-10
DOI: 10.23736/S0392-9590.18.03997-4

ORIGINAL ARTICLE

Electrical calf muscle stimulation in patients with post-thrombotic syndrome and residual venous obstruction after anticoagulation therapy

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ABSTRACT

BACKGROUND: The aim of this study was to assess the impact of electrical calf muscle stimulation (EMS) on clinical and ultrasound outcomes in patients with post-thrombotic syndrome (PTS) and residual venous obstruction (RVO).

METHODS: This was a prospective, comparative, non-randomized clinical trial involving patients who had completed a standard 6-month course of anticoagulation therapy for a first episode of unprovoked femoro-popliteal DVT and had signs of RVO in the affected veins and PTS as shown by a Villalta Score of >5. A blinded outcome assessor performed the ultrasound evaluations. A total of 60 patients in the age range from 40 to 86 years (mean 58.5±11.4) consisting of 38 men and 22 women were enrolled. They were divided into two groups of 30 participants each. Both groups (experimental and control) were treated by active walking, below-knee graduated compression stockings, and micronized purified flavonoid fraction. In the experimental group, EMS with «Veinoplus VI» device (three applications for 30 min every day) was also used. The patients were followed for 12 months with monthly DUS to reveal recurrent DVT and changes in RVO. The clinical criteria for treatment efficacy included changes in Villalta, VCSS and CIVIQ-20 scores.

RESULTS: Recurrent DVT was found in seven of 30 patients in the control group and in zero of 30 patients in the experimental group (23.3% *versus* 0%, P=0.01). Through the follow-up period the degree of RVO decreased in all affected veins in both groups (P<0.01). The most significant changes were found in the popliteal vein; 60.8% decreased to 28.8% in the experimental group and 50.9% to 27.3% in the control group (P<0.01) with significant differences between the groups (P<0.01). VCSS, Villalta and CIVIQ-20 scores also significantly decreased in both groups (P<0.01). In the group with EMS, changes in the current parameters were more intensive (P<0.01).

CONCLUSIONS: There is an ongoing process of deep vein recanalization during the 12 months after anticoagulant therapy cessation. Use of EMS in PTS treatment allows for reduction of recurrent DVT rates, increase the speed of deep vein recanalization and leads to additional improvement in the clinical PTS outcomes.

(*Cite this article as:* Lobastov K, Ryzhkin V, Vorontsova A, Schastlivtsev I, Barinov V, Laberko L, *et al.* Electrical calf muscle stimulation in patients with post-thrombotic syndrome and residual venous obstruction after anticoagulation therapy. Int Angiol 2018;37:400-10. DOI: 10.23736/S0392-9590.18.03997-4)

KEY WORDS: Post-thrombotic syndrome - Electric stimulation therapy - Prevention and control.

Deep vein thrombosis (DVT) is a vascular pathology that is associated with high morbidity and mortality rates worldwide. According to the official statistics from 2012 to 2014 in Russia, the annual incidence of DVT was estimated as 1.5 to 1.6 cases per 1000 persons per year.[1, 2] These figures exceed the international epidemiological data that has evaluated the incidence of DVT as 0.9 to 1.2 cases per 1000 persons per year.[3-5] Most of the physicians dealing with venous thromboembolism (VTE) are usually focused on prevention and treatment of pulmonary embolism (PE) and recurrent DVT, and less attention is typically paid to the post-thrombotic syndrome (PTS). At the same time, despite adequate anticoagulation, signs of PTS could be found in 20-50% of patients at two years after DVT with the maximal increase in morbidity after the first six months.[6, 7] According to a Russian epi-

demiological study, PTS prevalence in the general Russian population may be as high as 1.4%.[8] To the date, the primary tool for PTS diagnosis is the Villalta Score, which considers the subjective symptoms and objective signs of chronic venous disease (CVD). The presence of five scores confirms the diagnosis of PTS, and ≥15 scores indicate the development of a severe disease.[6, 9, 10]

The basic pathological mechanism of PTS development is increased ambulatory venous pressure (AVP), which causes the microcirculation overload and appearance of symptoms.[11, 12] An increase in AVP appears to be due to residual venous obstruction (RVO) and/or valvular incompetence of the affected veins in addition to a combination of these two mechanisms.[13] It has been shown that the presence of RVO at six months after DVT is a stronger predictor for PTS than the presence of isolated deep vein reflux.[14, 15] Moreover, the risk of recurrent DVT in the presence of RVO can be increased 2-25 times.[16-20]

Adequate anticoagulant therapy for the primary DVT can prevent extension of thrombi and reduce the threat of potentially fatal PE but is not responsible for the process of deep vein recanalization. It has been shown that after 3 to 6-month period of vitamin K antagonist (VKA) treatment, RVO signs can be detected in 38-61% of patients with proximal DVT.[18, 19] In addition, the recanalization process does not stop after the anticoagulant therapy cessation and can last up to 36 months.[19]

Thus, there is a challenge to increase deep vein recanalization with some different treatment approaches. Previously, it has been shown that mobilization in the presence of elastic compression is a good and safe treatment modality for preventing PTS in patients with proximal DVT.[21] Also, it has been established that muscle contraction can activate the fibrinolytic system, and high values of endothelial shear stress are associated with increase in angioprotective, anti-inflammatory, anticoagulant, and antisclerotic properties of endothelial cells.[22, 23] From this point of view, mechanical methods that accelerate blood outflow from lower limbs may be useful in DVT and PTS treatment. Among different mechanical approaches, portable devices for electrical calf muscle stimulation (EMS) have particular prospects. In previous studies, it has been shown that modern EMS devices can significantly increase the velocity of venous blood outflow, reduce subjective symptoms and objective signs of chronic venous diseases, and decrease the incidence of postoperative VTE.[24-28]

This study aimed to assess the impact of electrical calf muscle stimulation on clinical and ultrasound outcomes in patients with RVO and PTS after cessation of standard anticoagulant therapy.

Materials and methods

This was a prospective comparative parallel non-randomized clinical trial with blind ultrasound outcome assessor which took part in three clinical centers in Moscow in the period from 2013 to 2016: Clinical Hospital 1 of the President's Administration of Russian Federation (center 1); Central City Hospital of Ivanteevka (center 2); and Moscow Clinical Hospital 24 (center 3).

Inclusion criteria included several parameters: 1) age >18 years; 2) the first episode of clinically unprovoked DVT that obligatory involved popliteal vein and optionally extended into the femoral or common femoral veins as confirmed with duplex ultrasound (DUS); 3) complete standard 6-month course of anticoagulant therapy; 4) presence of residual venous obstruction (RVO) of the popliteal vein, and/or femoral vein, and/or common femoral vein; 5) the presence of PTS (≥5 Villalta Score); and 6) informed consent given.

Exclusion criteria included several parameters: 1) extension of the primary thrombus into iliac vein; 2) isolated calf vein thrombosis; 3) implanted inferior vena cava filter; 4) indication for prolonged anticoagulant therapy; 5) indication for prolonged (>1 month) use of parenteral anticoagulants; 6) indication for dual antiplatelet therapy; 7) Ankle-Brachial Index <0.5; 8) severe trophic changes on lower limbs (5-6 clinical classes according to the CEAP); 9) infection of lower limb soft tissues; 10) an implanted pacemaker; 11) impossible for patient to walk 5000 steps a day; 12) trauma occurred during the observation period and was accompanied by lower limb immobilization; 13) major surgery or any venous surgery performed during the observation period; 14) inpatient treatment with bed rest for >3 days during the observation period; 15) malignancy as revealed during the observation period; and 16) low study compliance. The conditions of the study allowed long-term use of only one antiplatelet drug (acetylsalicylic acid [ASA] in a dose up to 100 mg per day or ticlopidine at a dose of 75 mg per day).

Before enrolling, all patients underwent clinical and ultrasound examinations, which included collection of demographic data, complaints, medical history, general clinical examination, the clinical/etiology/anatomy/pathophysiology (CEAP) clinical class determination, CVD severity according to the revisited Venous Clinical Sever-

ity Score (VCSS),[29] PTS severity according to the Villalta Score,[9] quality of life according to the CIVIQ-20 questionnaire[30] in addition to detection of RVO with bilateral compression DUS. RVO was defined as the presence of residual thrombotic masses occupying >20% of the vein cross-sectional diameter. To determine RVO, compression DUS was performed with the patient in the horizontal position. Compressibility of the common femoral and femoral vein (CFV and FV, respectively) were assessed in the supine position, and the compressibility of the popliteal vein (PV) was assessed in the prone position. RVO evaluation was performed at the narrowest visible point of the vein. RVO degree was calculated as the ratio of vein cross-sectional diameter with maximal compression to the diameter without any compression at the same point: ($d_{compression}$ / $d_{without\ compression}$) x 100% (Figure 1). Each measurement was repeated three times, and the mean value was used in all calculations. RVO extension was assessed by the modified Marder Score[31] (Figure 2).

After informed consents were signed, the patients were allocated to the experimental or control group depending on the center at which they were examined. Participants were enrolled in the experimental group at center 2 and into the control group at center 1. Active walking with a target number of steps ≥5000 per day was recommended for patients in both groups. To control the daily number of steps, the individual electro-mechanical pedometer "OMRON HJ-005" (Omron, Shangai, China) was used. Also, all participants were instructed to use below-knee elastic compression stockings (ECS) daily with a pressure of 23 to 32 mm Hg and to take micronized purified flavonoid fraction (MPFF) 500 mg bid for two months regularly twice a year.

The patients in the experimental group also underwent EMS with a portable "Veinoplus V.I." device (Ad Rem Technology, France). The device generates low frequency (250 Hz) alternating electrical current with modulated periods of impulse duration (from 25 to 240 μs), which results in short lasting (50 ms) muscle contractions with a frequency of 60 to 100 min^{-1} per 30 min session. It consists of a handheld central unit that works on a battery, connected to two ovoid skin adhesive electrodes. The two electrodes of the device are positioned symmetrically on the mediocentral part of the calf. During the study, it was recommended that patients use EMS of both legs while not wearing ECS three times per day (morning, afternoon, and evening) with the maximum tolerated power and mandatory achievement of effective plantar flexion in the ankle joint. Application of both electrodes is necessary for clos-

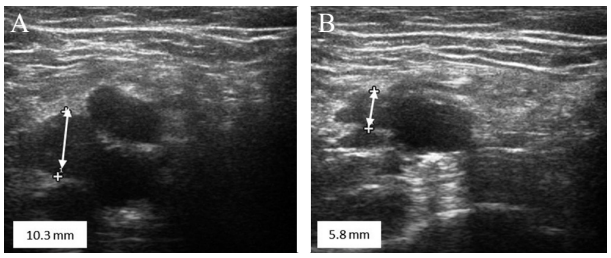

Figure 1.—Method for determining residual venous obstruction (RVO). Example of calculation of the superficial femoral vein: A) vein cross-sectional diameter without compression; B) vein cross-sectional diameter with maximal compression.
RVO = 5.8 / 10.3 x 100% = 56%.

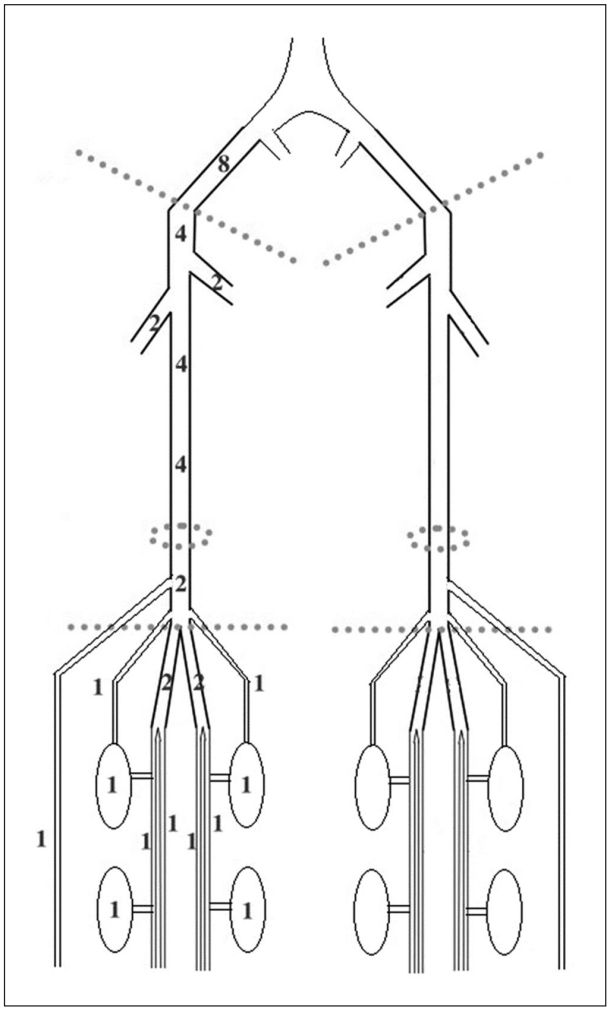

Figure 2.—Modified Marder Score.

ing the electrical circuit. It is possible to apply them to the single extremity, but the hemodynamic or clinical effects of such positioning were not studied previously. To avoid unpredictable results, we decided to use the standard application on both legs as was recommended by the manufacturer. At the first visit, participants were taught how to use the "Veinoplus V.I." Also, the preferred stimulation power was determined. After that, the procedure details in addition to the stimulation power were registered in a specially designed log book. In addition, in the log book, the patient recorded the number of steps taken during the day, ECS use, and amount of MPFF taken. At each visit, the investigator studied the personal patient log book. He compared the number of registered EMS procedures with the indicator in the device, which has an integrated counter of completed sessions. The investigator also evaluated the adequacy of the stimulation power used for the last procedure. Patients in the control group maintained a similar log book without registration of EMS sessions.

Data extracted from the individual log books were also used to calculate the patient's adherence to the treatment protocol. Compliance with the compression stockings was calculated as the ratio of all days on which patients used ECS to the total days of follow-up (365 days if the patient reached the end of the study). Compliance with EMS was calculated as the ratio of all performed sessions to the total number of prescribed sessions (1095 sessions during the 12-month follow-up). Compliance with MPFF use was evaluated as the ratio of all days when the patient took the drug to the number of recommended days (120 days during the 12-month follow-up).

All patients were followed-up for 12 months with monthly visits. At every visit, the investigator performed a clinical examination, studied medical records for the past period with maximal attention to the possible symptoms of recurrent venous thromboembolism, acute illnesses, surgery, injuries, hospitalization, assessed the individual log books, and evaluated the results of DUS obtained by a blinded ultrasound outcome assessor. Baseline and monthly DUS sessions were performed at center 3 by one specialist who did not have information about the patient's treatment protocol or the results from the previous scanning. DUS was performed every month in order to exclude silent DVT recurrence and at baseline, six, and 12 months to reassess both RVO degree and extension. Clinical outcomes such as VCSS, Villalta, and CIVIQ-20 scores and changes in CEAP clinical class were assessed by the investigator at baseline, six, and 12 months.

The primary study endpoint included absence of symptomatic or asymptomatic recurrent DVT, absence of symptomatic PE. The secondary study endpoints included reductions in the RVO degree and RVO extension according to the modified Marder Score, reduction in disease severity according to the VCSS and Villalta scores, improvement in the quality of life according to the CIVIQ-20 scores, and absence of CVD progression according to changes in the CEAP clinical class.

Symptomatic recurrent DVT was considered if pain, edema, redness on the affected limb suddenly increased, or classical symptoms of DVT appeared in the contralateral limb. The ultrasound criteria for DVT recurrence included the re-occlusion of previously recanalized venous segments in addition to occurrence of thrombotic occlusion on previously intact veins on the affected limb, or new venous occlusions on the contralateral limb. Due to the blinding of the ultrasound outcome assessor, final registration of DVT recurrence was done by the investigator after comparison of serial scans.

The study protocol was approved by the local Ethical Committee of Pirogov Russian National Research Medical University.

Statistical analysis

Statistical analysis was done with the IBM SPSS Statistics v.19 package. A preliminary calculation of the sample size was not available because there was no reliable information on the primary endpoints' magnitude and the possibility of EMS influence on their changes. Thus, a preliminary assessment of the study results was planned with a sample size of 60 participants (two groups of 30 patients in each group). Based on these results, statistically significant differences were obtained that allowed the study to be completed and conclusions to be drawn. Data distribution was checked with the Kolmogorov-Smirnov test. All numerical values were represented as the mean±standard deviation (M±σ). Comparison of the means was carried out using a *t*-test for independent samples and a comparison of the relative values using a two-sided Fisher Exact Test. The significance of dynamic changes in the mean values was obtained from the generalized linear model repeated measures (GLM RM). As a within-subject factor time (baseline, six, and 12 months) was used and group (either experimental or control) was used as a between-subject factor. As a result, three P values were calculated: 1) the within-subject factor (time); 2) the within-subject interaction (time*group); and 3) the between-subject factor (group). The confidence interval (CI) for the relative values was calculated using the Wilson method. To com-

pare the cumulative incidence of reaching the endpoint, Kaplan-Meier statistics and the Log-Rank Test were used. P<0.05 was assumed as statistically significant.

Results

Patients had been enrolled in the study from 2013 to 2015. During this time, a total of 137 subjects with the first episode of unprovoked femoro-popliteal DVT, that obligatory involved popliteal vein, in most cases involved femoral vein and calf veins, sometimes involved common femoral vein, had completed the standard 6-month course of anticoagulant therapy and were examined. RVO signs were detected in 95 cases (69.3%; 95% confidence interval [CI]: 61.1-76.4%), and signs of PTS were observed in 75 cases (54.7%; 95% CI: 46.3-62.8%). Thus, 75 patients were invited to take part in the study, and five of them rejected the invitation. Seventy participants finally were enrolled. During the follow-up period, 10 patients withdrew from the study in accordance with the exclusion criteria: 1) two patients showed low compliance with EMS; 2) three patients could not walk >3000 steps per day; 3) in one subject, percutaneous coronary intervention was performed that required double antiplatelet therapy; 4) in one subject malignancy was diagnosed two months after enrolment; 5) one participant underwent major abdominal surgery; 6) a lower limb fracture with immobilization occurred in another participant; 7) and the last one was dropped from the study due to non-attendance at follow-up visits.

Thus, the final analysis included data on 60 patients with 30 subjects in each of the experimental and control group. All patients completed the standard 6-month course of treatment with oral anticoagulants, including oral rivaroxaban (63.3% of patients) and warfarin (36.7% of patients). Rivaroxaban was prescribed more often in center 1, so the number of patients finishing treatment with the novel oral anticoagulant was significantly higher in the control group (90% *versus* 36.7% in the experimental group). However, the groups were comparable according to the age, sex, CEAP clinical class, and localization of the primary lesion (Table I). The mean age was 58.5±11.4 years, males prevailed over females (63.3% *versus* 36.7%), and there were no significant differences between left- and right-side lesions (48.3% and 51.7%, respectively). Among the clinical class of CVD, chronic venous edema (C3 class) was observed in most of the patients (66.7%). Regarding the severity of CVD and PTS, the patients in the experimental group were characterized with more progressive dis-

TABLE I.—*Patients' baseline characteristics.*

Characteristics	Experimental group (N.=30)	Control group (N.=30)	P
Age (M±σ), years	61.0±9.1	55.9±12.9	0.080
Males (%)	60.0	66.7	0.395
Distribution according to CEAP clinical classes (%)			
C2	0.0	3.3	0.257
C3	60.0	73.4	
C4	40.0	23.3	
VCSS Score (M±σ)	9.9±1.6	8.3±2.7	0.007
Villalta Score (M±σ)	18.9±3.9	12.0±6.2	<0.0001
CIVIQ-20 Score (M±σ)	67.8±8.4	47.1±19.6	<0.0001
Rivaroxaban in treatment of index DVT (%)	36.7	90.0	<0.0001
Lesion at the left side (%)	46.7	50.0	0.5
Presence of RVO at different venous segments (%)			
CFV	13.3	26.7	0.333
FV	13.3	40.0	0.039
PV	100.0	100.0	-
Degree of RVO at different venous segments (M±σ)			
CFV	47.2±14.3	48.3±14.9	0.903
FV	54.8±23.6	52.5±21.5	0.862
PV	60.8±17.5	49.6±21.4	0.030
Marder Score (M±σ)	5.6±2.8	5.6±3.5	0.935
Acetylsalicylic acid intake (%)	36.7	30.0	0.392
Steps per day (M±σ)	6598.5±558.2	6783.9±1094.9	0.413
Adherence to the ECS (M±σ)	91.9±5.9	93.4±6.2	0.351
Adherence to the MPFF(M±σ)	98.3±9.1	96.7±12.7	0.561
Adherence to the EMS (M±σ)	91.2±5.3	-	-

ease and more affected quality of life as reflected by an increased Villalta, VCSS, and CIVIQ-20 scores (Table I).

With respect to both RVO degree and extension, patients were well-matched according to the Marder Score (5.6±2.8 and 5.6±3.5 in the experimental and control groups, respectively). At the same time, lesions at the femoral vein were more often observed in the control rather than the experimental group. RVO at the popliteal vein was detected in all patients but was more intensive in patients in the experimental group (Table I). Adherence to the treatment protocol exceeded 90% in both groups.

All of the patients included in the final analysis were followed for 12 months. No episodes of symptomatic PE were observed. Recurrent DVT was found in seven control patients and in none of the experimental ones (23.3%; 95% CI: 11.8-40.9% *versus* 0%; 95% CI: 0-11.4%), P=0.011. It is important that symptomatic DVT recurrence was observed only in two cases and was represented by great saphenous vein thrombosis that extended into the common femoral vein and medial plantar vein thrombosis that extended into the posterior tibial veins. Asymptomatic DVT recurrences were detected in five patients who had undergone routine DUS and presented with PV re-occlusion in three cases. Re-occlusion of the posterior tibial veins was detected in one case, and thrombosis of the previously intact calf muscle vein was detected in the last case. In all observations, the recurrent DVT had ipsilateral localizations. The new thrombotic events were detected during the first month after discontinuation of anticoagulation in three patients, during the second month in two cases, and at the fifth and seventh months in the last two cases. This corresponds to seven, eight, eleven and thirteen months after the primary DVT, respectively. Thus, an overwhelming number of recurrent DVTs occurred within the first six months after anticoagulant therapy was completed (Figure 3).

In the analysis of RVO changes, the intact and re-occluded venous segments were excluded. So, for the calculations were used only significant values of RVO (from 20% to 100%) as long as there was no increase in the RVO value due to recurrent DVT. The results showed a significant decrease in the degree of RVO in all venous segments throughout the whole observation period. These findings correspond with the active process of deep veins recanalization after the cessation of standard anticoagulant therapy (Table II). There were no significant differences between the groups in the speed of recanalization at the CFV and FV while using EMS at the PV allowed us to improve patency more significantly (Figure 4). Moreover, total RVO extension, as assessed with the modified Marder Score, decreased more rapidly and intensively in the patients that underwent EMS (Figure 5). In the experimental group, the mean Marder Score decreased from 5.6±2.8 to 2.9±3.0 (1.9-fold) and in the control group, a decrease from 6.2±3.4 to 4.7±3.5 (1.3-fold) occurred, P=0.048. Thus, the use of EMS allowed achieving a more complete recanalization during the 12-month follow-up.

ASA, at a dose of ≤100 mg daily, was taken by 36.7%

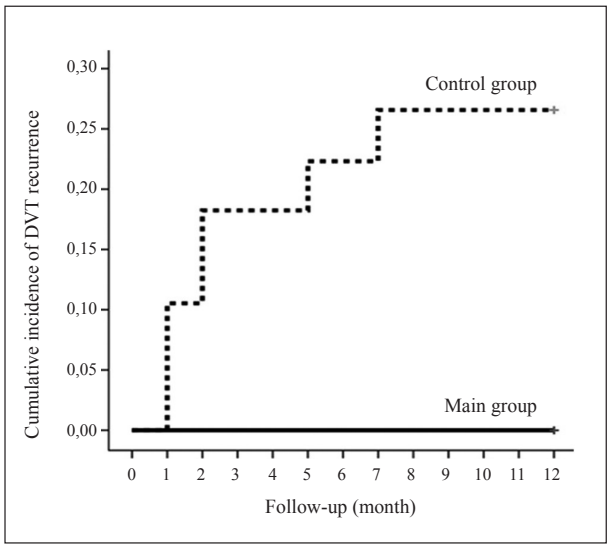

Figure 3.—Cumulative rate of recurrent deep vein thrombosis.

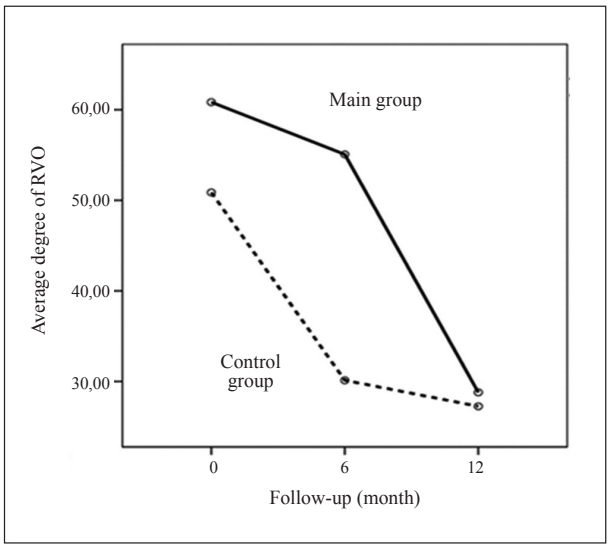

Figure 4.—The dynamic in RVO at the popliteal vein.

TABLE II.—*Dynamic changes in the average degree of residual venous obstruction (RVO) (M±σ). Intact and re-occluded venous segments excluded.*

	N.	Follow-up			p_1	p_2	p_3
		0 month	6 months	12 months			
CFV							
Totally	11	47.8±14.8	36.4±16.3	22.2±19.7	0.0001	0.113	0.409
Experimental group	4	47.2±14,3	40.5±16.1	34.0±9.7			
Control group	7	48.1±16.1	34.0±19.0	15.4±21.3			
FV							
Totally	14	55.6±23.6	45.1±15.4	30.4±17.9	0.003	0.562	0.773
Experimental group	4	54.7±23.6	44.5±13.9	37.5±3.5			
Control group	10	56.0±20.8	45.4±16.6	27.6±20.7			
PV							
Totally	53	56.5±14.6	44.2±21.6	28.1±18.8	0.0001	0.0001	0.004
Experimental group	30	60.8±16.5	55.1±14.6	28.8±19.0			
Control group	23	50.9±20.1	30.1±21.3	27.3±18.9			
Marder Score							
Totally	53	5.9±3.0	4.7±3.3	3.7±3.4	0.0001	0.048	0.158
Experimental group	30	5.6±2.8	4.3±2.8	2.9±3.0			
Control group	23	6.2±3.4	5.4±3.8	4.7±3.5			

p calculations are based on the generalized linear model repeated measure (GLM RM).
p_1: within-subject factor "time"; p_2: within-subject interaction "time * group"; p_3:between-subject factor "group".

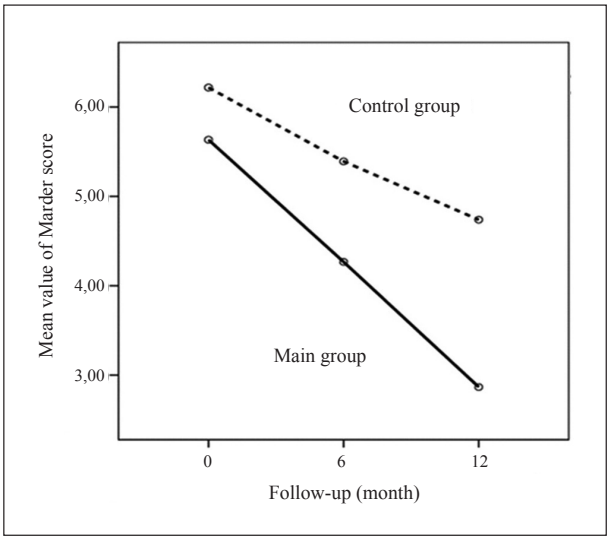

Figure 5.—The dynamic in Marder Score.

and 30% of subjects in the experimental and control groups, respectively, during the follow-up. Administration of the drug did not have any significant effects on treatment outcomes as recurrent DVT was observed in 10% (95% CI: 2.8-30.1%) of patients taking ASA and in 12.5% (95% CI: 5.5-26.1%) of those who did not use the drug (P=1.0). Kaplan-Meier statistics showed with equal reliability that EMS use reduced the incidence of recurrent DVT both in patients who used and did not use antiplatelets (P=0.006). Similarly, ASA use did not influence the dynamics of changes in RVO at PV in GLM RM (P=0.962).

Clinical outcomes of the treatment were analyzed in patients who were free of recurrent DVT (N.=53), and the results are presented in Table III. Proposed therapeutic modalities led to a significant decrease in VCSS, Villalta, and CIVIQ-20 scores that was observed in both groups with significant differences between them (P=0.0001). The changes in these indices were more pronounced in the EMS group in comparison with the control group; decreases in VCSS Score of 1.6-fold *versus* 1.1-fold (control), Villalta Score 2.3-fold *versus* 1.2-fold, and CIVIQ-20 Score 1.7-fold *versus* 1.0-fold were observed. Thus, the addition of EMS to the standard PTS therapy may lead to additional improvement in clinical outcomes.

As for the CEAP clinical class, its changes were not observed in any of the experimental or control patients. At the twelfth month of observation, at which point patients with recurrent DVT were excluded, class C3 was identified in 66% of the cases and C4 in 34% of the cases.

Discussion

This is the first published study that evaluates the impact of a modern portable device for electrical calf muscle stimulation on the clinical and ultrasound outcomes of standard

TABLE III.—*Dynamic changes in the clinical post-thrombotic scores (M±σ) in free of recurrent deep vein thrombosis patients.*

	Follow-up			p_1	p_2	p_3
	0 month	6 months	12 months			
VCSS						
Totally	9.1±2.4	7.6±1.8	6.5±1,8	0.0001	0.0001	0.391
Experimental group	9.9±1.6	7.8±1.6	6.1±1.5			
Control group	8.1±2.8	7.3±2.1	7.1±2.1			
Villalta						
Totally	16.2±6.1	12.0±4.8	9.1±4.2	0.0001	0.0001	0.109
Experimental group	18.9±3.9	12.8±4.0	8.2±2.7			
Control group	12.7±6.7	10.9±5.6	10.2±5.4			
CIVIQ-20						
Totally	59.3±17.1	49.3±13.1	43.2±13.7	0.0001	0.0001	0.118
Experimental group	67.8±8.4	51.3±8.4	40.0±10.5			
Control group	48.2±19.3	46.7±17.3	47.4±16.2			

p calculations are based on GLM RM.
p_1: within-subject factor "time"; p_2: within-subject interaction "time * group"; p_3: between-subject factor "group".

conservative PTS treatment. There are a few important aspects of the study that need to be discussed, including the role of EMS in the prophylaxis of recurrent DVT, the influence of EMS on the deep vein recanalization, EMS capabilities in reducing signs and symptoms of PTS, and study limitations.

Recurrent DVT

To date, the primary method for recurrent VTE prevention is prolonged anticoagulant therapy.[32] Meanwhile, long-term use of VKA allows a 5-fold reduction in VTE recurrence risk with a 2.5-fold increase in major bleeding risk.[33] The novel oral anticoagulants (rivaroxaban, apixaban, dabigatran) that have become available in recent decades are safer when compared with VKA,[34] but their risk/benefit ratio is limited with a maximum of 36 months of continuous use.[35] In addition to anticoagulants, other antithrombotic drugs such as ASA and sulodexide may be used for secondary VTE prevention after cessation of standard anticoagulant therapy.[36, 37] However, the capability of ASA to decrease the VTE recurrence risk is too weak when compared with oral rivaroxaban, and its risk profile is imbalanced.[38] The long-term use of the safest drug, sulodexide, in turn, has not been adequately assessed from the standpoint of pharmacoeconomics.

Thus, nowadays, rational decision-making for prolonged anticoagulant therapy and the choice of an adequate pharmacological agent is based on an individual patient's risk profile for the recurrent VTE and major bleeding.[32, 39] The most critical factors determining the threat of recurrent DVT and/or PE include clinically unprovoked index VTE, personal history of VTE, manifestation of index VTE with PE and/or proximal DVT, elevated D-dimer after cessation of anticoagulant therapy, RVO, resumption of estrogen-containing pills, male gender, and/or antiphospholipid antibodies.[40, 41]

An RVO, which persists after the completion of the standard course of anticoagulation, can play a particular role in provoking DVT. Different studies have demonstrated that in the presence of RVO, the risk of VTE recurrence can be increased up to 25 times, and prolonged anticoagulant therapy with VKA allows only for a reduction but not elimination, of this threat.[16-20] It is easy to assume that RVO creates unfavorable conditions for venous blood outflow, which is the reason that methods of active blood drainage such as EMS can provide some relief.

This study presents the first experience of EMS technology application in the prevention of recurrent VTE after cessation of standard anticoagulant therapy. Initially, the study implied an assessment of RVO changes in the EMS background. Therefore, inclusion criteria were used to determine the narrow scope of the technique. However, the unexpectedly high incidence of silent DVT recurrence was revealed, which allowed for reconsideration of use of EMS.

Features of the primary goal imposed many restrictions on the study in the field of DVT recurrence. First, only patients with clinical signs of PTS and a high Villalta Score were enrolled. This feature may reflect the unusual treatment compliance that exceeded 90%. It should be assumed that in the general population, compliance with EMS and elastic compression may be lower than in the presented trial.

Second, only patients with persistent RVO were enrolled in the study. They had an extremely high prevalence of si-

lent affected vein re-occlusion. According to the literature, the DVT recurrence rate in the first 12 months after cessation of standard anticoagulant therapy should be about 10%.[6] However, in patients with RVO, these figures may be as high as 27%.[16] Thus, it should be assumed that EMS efficacy in the general patient population, who were either positive or negative for RVO and/or PTS, may differ.

Third, the study did not assume patient stratification according to the risk of VTE recurrence and bleeding. Particularly, D-dimer levels[42-45] or other prognostic models such as the DASH Score,[46] Vienna predictive model,[47] and Men continue and HERDOO2 rule[48] were not taken into account.

Deep vein recanalization

To date, there is no clear definition of RVO. In a series of studies by Prandoni *et al.*, RVO was defined as a cross-sectional vein diameter with a >2 mm maximal compression at a single examination or 3 mm at two consecutive measurements.[14, 19, 20] Piovella *et al.* considered a residual intraluminal mass occupying >40% of the vein cross-sectional diameter as significant.[16, 18] Thus, there is a lack of consensus about the RVO threshold that may be clinically and/or hemodynamically significant. In the present study, we considered our criteria for significant RVO as residual masses occupying >20% of the vein cross-sectional diameter. This figure corresponded CFV and SFV diameters of about 2 mm and about 1 mm PV under maximal compression. Thus, our threshold was closer to Prandoni's approach. At the same time, all previous studies on RVO converge at the fact that if the vein represents residual obstruction at 3 to 6 months after the index DVT, it will never regain its former characteristics and may be a substrate for recurrent thrombosis and/or PTS development. Thus, today it is critical to find an optimal approach for the treatment of such patients.

The design of our study initially was aimed at investigating RVO outcomes. The hypothesis was that EMS could improve deep vein patency. The enrolled patients were first matched according to RVO degree and extension. To assess RVO extension, we used the modified Marder Score. Initially, this scale was used to evaluate thrombus burden in phlebography studies, but then it was found to be useful in ultrasound assessments of thrombus extension.[31, 49] Previously, we reported that the Marder Score shows good correlation with clinical PTS signs.[50] Based on the study results, both RVO degree and extension were reduced in both groups through the 12-month follow-up. However, additional EMS use allowed us to increase the speed of deep vein recanalization and achieve better vein patency. The most impressive results were observed at the popliteal vein, which was affected in all patients.

Symptoms and signs of PTS

It is well known that the incidence of PTS, including its most severe forms, steadily increases during the eight years after the index DVT.[6] The primary risk factor for PTS signs and symptoms appearance and worsening is ipsilateral recurrent DVT. At the same time, in our study, we found a definite decrease in PTS severity even in the background of standard therapy. There are several explanations for these findings. First, we excluded data from patients with recurrent DVT when we analyzed the proposed treatment's clinical efficacy. It should be assumed that if such silent recurrent DVTs were missed in the absence of serial DUS, these DVTs could have a negative impact on the clinical status and the results of utilizing the traditional therapeutic approach. At the same time, the use of active walking, ECS, and MPFF in the absence of recurrent DVT has significantly improved the clinical PTS signs even without EMS application. So, the main effort in the treatment of PTS should be made to prevent recurrent DVT. Second, the cause may lie with the unusually high treatment compliance that can be reflected in initially severe forms of PTS. Moreover, subjects in the experimental group had more progressive types of PTS and CVD that could have some influence on EMS efficacy. However, GLM RM did not show any significant between-subject interactions with respect to the Villalta, VCSS, and CIVIQ-20 scores. Thus, the indicated tendency toward better improvement of PTS symptoms and signs after EMS use should be valid.

Limitations of the study

The main limitations of the study are a small sample, lack of randomization, different approaches in the treatment of index DVT, incompatibility of patients according to PTS and CVD severity, the degree of RVO, and absence of patient's stratification according to the risk of recurrent DVT and major bleeding. However, this study shows a potential role for EMS in the prevention of recurrent DVT without increasing bleeding risks, in improving deep vein patency, and reducing the PTS signs and symptoms. Future trials should take into account the limitations of this study to determine the role of EMS in the treatment of PTS.

Conclusions

There is an ongoing process of deep vein recanalization during the 12 months after anticoagulant therapy cessation in patients with RVO and PTS. Use of EMS in PTS treatment allows for reduction of recurrent DVT rates, increase the speed of deep vein recanalization and leads to additional improvement in the clinical PTS outcomes.

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Conflicts of interest.— Kirill Lobastov: honoraria for lectures and travel grants from Bayer, Servier; Ilya Schastlivtsev: honoraria for lectures and travel grants from Bayer; Victor Barinov: honoraria for lectures and travel grants from Bayer, Servier; Leonid Laberko: honoraria for lectures and travel grants from Servier.

Funding.—The study was conducted with the technical support of "BEHO+" Ltd – the distributor of AdRem Technology in Russia. The Company provided the Veinoplus devices and individual pedometers for all patients. The Company did not influence collecting and analyzing data, making a decision on publication and preparing the manuscript.

Authors' contributions.—Kirill Lobastov: study design, data collection, statistical processing, writing the manuscript; Vladimir Ryzhkin, Athena Vorontsova and Ilya Schastlivtsev: data collection; Victor Barinov and Leonid Laberko: study design, editing the manuscript; Grigory Rodoman: editing the manuscript.

Congresses.—The parts of this study were presented at: 1) EVF 18th annual meeting, 2017, Porto, Portugal – e-poster awarded with prize; 2) ESVS 31st Annual Meeting, 2017, Lyon, France – oral presentation; 3) 59th ASH Annual Meeting and Exposition, 2017, Atlanta, GA, USA – oral presentation; 4) XVIII UIP World Congress, 2018, Melbourne, Australia – oral presentation.

Article first published online: August 28, 2018. - Manuscript accepted: July 11, 2018. - Manuscript revised: July 3, 2018. - Manuscript received: March 14, 2018.