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Effectiveness of the Frequency Rhythmic Electrical Modulation System for the Treatment of Chronic and Painful Venous Leg Ulcers in Older Adults

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Abstract

Frequency rhythmic electrical modulation system (FREMS) is an innovative type of transcutaneous electrotherapy used in a rehabilitation setting for the treatment of pain, especially in diabetic patients. In a randomized clinical trial, we tested the hypothesis that FREMS is effective in the treatment of chronic and painful venous leg ulcers in 20 older patients. Group A (10 patients) received FREMS and topical treatment, whereas group B (10 patients) received topical treatment alone. Over a period of 3 consecutive weeks, 15 treatment sessions were done for each group. Wound healing and tissue repair were evaluated with the Visitrack™ digital planimetry system and photos. Pain was evaluated using the Visual Analogic Scale (VAS). The measurements were done at baseline and after 5, 10, and 15 days of treatment, with follow-up measurements after 15 and 30 days from the last treatment session. Group A showed a statistically significant decrease in ulcer area during the treatment and follow-up. The VAS score showed a statistically significant decrease after 5 and 10 days of treatment. Group B showed a statistically decrease in ulcer area after 5, 10, and 15 days of treatment with a reduction of VAS score only at 15 days of follow-up. At the end of the treatment, the comparison of the change in ulcer area and the change in VAS score of each group showed a statistically significant difference between groups, suggesting the therapeutic and analgesic efficacy of FREMS in reducing pain and area of chronic venous leg ulcers in older adults. Further investigation is needed to determine its reproducibility in larger case series or randomized clinical trials with longer follow-up periods.

Introduction

Several putative therapeutic approaches for chronic leg ulcer treatment have been proposed, including the use of antiseptics, antibiotics, growth factors, pressurized oxygen, biologically engineered skin substitutes, and physical therapy modalities, such as ultrasound, electrical stimulation, and electromagnetic fields.[1–6] In particular, among physical therapy modalities, several studies have cited the use of ultrasound therapy, although a systematic review concluded that there is no strong evidence that therapeutic ultrasound speeds the healing of venous leg ulcers.[7] Furthermore, among alternative physical therapies for wound care management, electrotherapy and electromagnetic therapy were used to treat ischemic and diabetic ulcers and venous ulcers, respectively, with contrasting findings.[2] Electrical or electromagnetic stimulation can be useful to increase ulcer healing through their antibacterial effect, stimulating growth factors and collagen synthesis.[8,9] Pulsed magnetic field treatment may increase collagen production by altering cyclic adenosine monophosphate (AMP) metabolism.[10]

Among physical therapies that use electrical stimulation, frequency rhythmic electrical modulation system (FREMS) is an innovative type of transcutaneous electrotherapy used in the rehabilitation setting for the treatment of pain, especially in patients with diabetes mellitus.[11–14] This method uses sequences of modulated electrical stimuli that vary automatically in terms of pulse frequency, duration, and voltage amplitude. The FREMS method was designed on the basis of

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the hypothesis that the summation of subthreshold electrical stimuli, conveyed through the skin proximal to a motor nerve in a noninvasive system, would induce composite motor action potentials in excitable tissues through specific sequences of weak impulses, characterized by a rapid increase and decrease in pulse frequency and duration, which results in the gradual recruitment of membrane potentials in the stimulated tissues.[12,14]

This type of physical therapy showed good results in the treatment of diabetic neuropathy through a cutaneous microvascular flow increase after 10 sessions,[13] and with pain reduction increasing the antinociceptive threshold.[15,16] However, only one study suggested a possible role of FREMS in treating chronic leg ulcers.[17] Standard treatments of leg ulcers include mechanical and enzymatic debridement with various types of dressings.[5] Type, localization, and depth of ulcers, amount of necrotic tissue, and amount of exudate are the criteria that determine the kind of local therapy. The healing of ulcers is dependent upon a whole series of risk factors, including initial ulcer area, patient's age, gender, height, weight, mobility, wound location, wound exudate, the condition of the surrounding skin, and so on.[18] As seen above, the efficacy of physical therapy modalities, such as electrical stimulation and electromagnetic, is still discussed.[19] The purpose of this study was to examine the effectiveness of FREMS in the treatment of chronic and painful venous leg ulcers in older adults.

Materials and Methods

This study was a randomized clinical trial conducted according to the Declaration of Helsinki, the guidelines for Good Clinical Practice, and the Consolidated Standards of Reporting Trials (CONSORT) Statement guidelines (available at www.consort-statement.org/). This study was approved by the Institutional Review Board (IRB) of the University of Foggia, Foggia, Italy. Consecutive outpatients older than 65 years of age and with a variable number of chronic and painful leg ulcers (arterial leg ulcers, venous leg ulcers, mixed arterial and venous leg ulcers, and diabetic leg ulcers), attending the Department of Plastic and Reconstructive Surgery and the Department of Physical Medicine and Rehabilitation, University of Foggia, Foggia, Italy, from January, 2010, to July, 2010, were invited to participate in the study and were screened for study eligibility. Clinical signs and ankle-brachial pressure index (ABPI) were used to exclude arterial (ABPI <0.8) and mixed arterial and venous leg ulcers (clinical signs of varicose vein and ABPI <0.8).[20] Hyperglycemia (>126 mg/dL) and a clinical diagnosis of diabetes mellitus were used for diagnosing diabetic ulcers. Patients less that 65 years of age, those with diabetes mellitus, neoplastic pathology, central neurological diseases, renal diseases; with a pacemaker, defibrillator, or neurostimulator; and undergoing chemotherapy were excluded from the study. All chronic venous ulcers in these patients were located below the level of the knee. The patients had not been previously treated with medical or physical therapies.

A total of 40 consecutive outpatients (23 women and 17 men) were screened for study eligibility. At the end of the evaluation, 20 patients with painful venous leg ulcers who fulfilled the selection criteria and agreed to participate, were enrolled in the study (11 females and 9 males; mean age [standard deviation, SD]: 72.9 (5.6) years). Written informed consent was obtained from all subjects and/or their relatives. Reasons for exclusion are shown in Fig. 1, which is a flow diagram of subject recruitment and retention. These participants were randomly assigned to two groups: A group of 10 patients (6 females and 4 males) received FREMS and topical treatment (group A) and a group of 10 patients (5 females and 5 males) received topical treatment alone (group B or control group). Concealed allocation was performed with random numbers generated from the website www.random.org/ before the beginning of the study. The Random Integer Generator procedure allowed us to generate random integers. A priori, it generated 100 random integers and, before the beginning of the study, the randomization number was already present. Individual, sequentially numbered index cards with the random assignments were prepared. The index cards were folded and placed in sealed opaque envelopes. A physician who was unaware of the baseline examination findings opened the envelopes to attribute the interventions according to the group assignments.

Both groups received a total of 15 treatment sessions over a period of 3 consecutive weeks (5 days per week). The first step of treatment was cleaning the ulcers with saline water. Then, group A received FREMS administrated through the device model Aptiva Ballet (Lorenz Therapy System, Lorenz Biotech, Medolla, Italy). The machine was equipped with four desynchronized and independent channels with two pairs of electrodes (red positive [+] and black negative [−]). An electrical signal was sent through small transcutaneous electrodes. The impulse amplitude of the signal was preset by the operator using a remote control to the maximum value according to the patient's sensitivity threshold of the stimulated tissue. Channel 1 was usually applied to the calf or anterior tibial muscle following the tibial arterial, positioning the (+) electrode on the muscle venter and the (−) one on the tendinous muscle insertion. Channel 2 was applied on a part of healthy and well-cleaned tissue around the leg ulcer. The position of this electrode was changed at each session, usually a few millimeters from left to right around the ulcer. Channel 3 was applied under each malleolus, positioning the (+) electrode on the internal side of the ankle, and the (−) electrode on the lateral malleolus. Channel 4 was set up by placing the (+) electrode on the back and the (−) one on the sole of the foot. The patients received FREMS for 25 min. In the present study, the protocol used was recommended by the manufacturer and guidelines of good clinical practice.[14,17]

After FREMS treatment, the patient's wounds were treated topically with antiseptic (collagenase/chloramphenicol) and a hydroalginate and covered with an elasto-compressive bandage. Group B received topical treatment alone for a total of 15 treatment sessions over a period of 3 consecutive weeks (5 days per week), with a change of dressing at each treatment session. For both groups, no compression therapy was used. The areas of the leg ulcers and tissue repair (fibrin accumulations, exudate, granulation, and epithelization) were evaluated with the employment of the Visitrack™ digital planimetry system and photos. The ulcer border was reproduced onto an acetate paper, first manually and afterward onto a digital tablet, which then calculated the area. The methods had a high consistency of results with each other, at least for ulcers with an area up to approximately

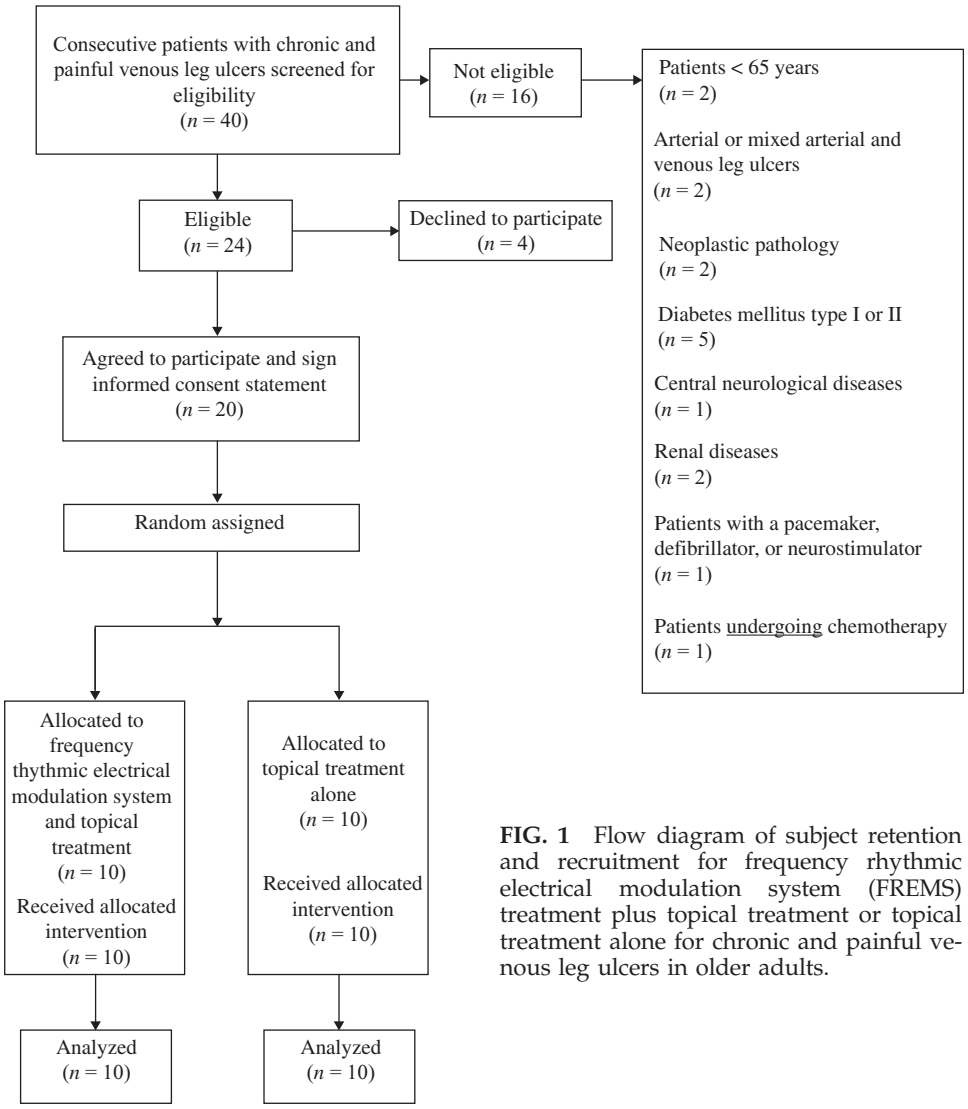

FIG. 1 Flow diagram of subject retention and recruitment for frequency rhythmic electrical modulation system (FREMS) treatment plus topical treatment or topical treatment alone for chronic and painful venous leg ulcers in older adults.

$10\,cm^2$.[21] Pain was evaluated by Visual Analogic Scale (VAS),[22] with a10-cm horizontal axis between a left end point of "no pain" and a right end point of "worst pain ever." The distance was measured, and pain was recorded on a 10-point scale. The outcome assessors were blind to treatment group assignment.

Statistical analysis

At baseline, differences in age, duration of ulcers, VAS score, and ulcer area between treatment groups were analyzed by the Mann–Whitney U-test, except for sex (Pearson chi-squared with Yates correction). Ulcer area and pain were monitored clinically at the beginning (t_0), after 5 (t_1), 10 (t_2), 15 days of administrated therapy (t_3) and after 15 (t_4) and 30 (t_5) days of follow-up. One-way analysis of variance (ANOVA) was used to determine differences (t_1-t_0, t_2-t_1, t_3-t_2,t_4-t_3, and t_5-t_4) in all outcome measures (VAS and leg ulcer area) in both treatment groups. The difference between baseline (t_0) and posttreatment outcome measure scores (t_1-t_2-t_3-t_4-t_5) for each group was computed by the Wilcoxon signed-rank test. The difference between each treatment group was performed by the Mann–Whitney U-test. The comparison between the change in leg ulcer area and the change in VAS score of each treatment group was analyzed by the Mann–Whitney U-test. GPower 3.1.10 software was used for power analysis and sample size estimation. All other analyses were performed using SPSS for Windows, version 6.1. The level of statistical significance was set as $p < 0.05$.

Results

A sample of 10 patients in each group achieved a power of over 80% to detect a difference of 3.5 points of VAS score between the two measurements t0 and t3, assessing SD = 1, correlation = 0.7, and alpha = 0.05. Table 1 summarizes the baseline clinical and demographic characteristics of the patients enrolled in the study. There were no significant between-group differences at baseline in the sex and age distribution, VAS score, time duration, and area of leg ulcers.

Table 1. Demographic and Clinical Characteristics at Baseline of Older Patients with Painful Venous Leg Ulcers Treated with Frequency Rhythmic Electrical Modulation System (FREMS) Plus Topical Treatment (Group A) or Topical Treatment Alone (Group B)

	Group A	*Group B*	p *value*
Mean age, years (SD)	73.1 (5.6)	72.7 (5.5)	0.07[a]
Sex (female/male)	6/4	5/5	0.97[b]
Duration (months)	6 ± 1.24	5.8 ± 1.03	0.74[a]
Visual Analogic Scale	9.1 ± 1.05	9 ± 1.05	0.91[a]
Area of leg ulcers (cm^2)	9.11 ± 2.02	9.89 ± 2.02	0.43[a]

[a]Mann–Whitney U-test.
[b]Pearson chi-squared test with Yates correction.
SD, Standard deviation

None of the patients reported adverse effects during the period of their participation in the study. All the 20 enrolled patients completed the trial and were included in the analysis. Figure 2 shows the course of a painful leg ulcer in one patient after FREMS and topical treatment. Table 2 shows the mean area of leg ulcers (Fig. 3) and the mean VAS score (Fig. 4) in both groups. In group A, the analysis showed a statistically significant decrease for the area of leg ulcers evaluated at 5, 10, and 15 days of treatment, and after 15 and 30 days of follow-up ($p < 0.05$). The VAS score showed a statistically significant reduction after 5 and 10 days of treatment ($p < 0.05$). In group B, the analysis showed a statistically significant reduction of area of leg ulcers after 5, 10, and 15 days of treatment ($p < 0.05$), whereas at 15 and 30 days of follow-up, the analysis of the area of leg ulcers did not show any improvement. VAS score improved only at 15 days of follow-up ($p < 0.05$).

Table 3 shows the results of the between-group analysis. The decrease in the area of the leg ulcers was statistically significant in group A in comparison with group B after 10 days ($p < 0.04$) and 15 days of treatment, and at 15 and 30 days of follow-up ($p < 0.005$) (Fig. 3). VAS score reduction was statistically greater in group A in comparison with group B after 5, 10, and 15 days of treatment and after 15 and 30 days of follow-up ($p < 0.05$) (Fig. 4). Finally, at the end of treatment, the comparison of the change in area of leg ulcers (mean of differences: Group A [t3-t0] = 5.26 ± 1.9 cm^2 and group B (t3-t0) = 2.43 ± 1.2 cm^2] (Fig. 5) and the change in VAS score (mean of differences: Group A [t3-t0] = 7.5 ± 1.27 points and group B [t3-t0] = 2.4 ± 1.17 points] (Fig. 6) of each group showed a statistically significant difference between groups ($p = 0.0005$ and $p = 0.0000$, respectively).

Discussion

The present study compared the results obtained after 15 treatment sessions over a period of 3 consecutive weeks using two different treatment regimes in patients with chronic and painful venous leg ulcers. The group of patients treated with FREMS and topical treatment showed a greater reduction in pain and an improvement of epithelization of ulcers compared with the group treated with topical treatment alone. There was a significant difference in change after 15 treatments sessions over a period of 3 consecutive weeks from baseline.

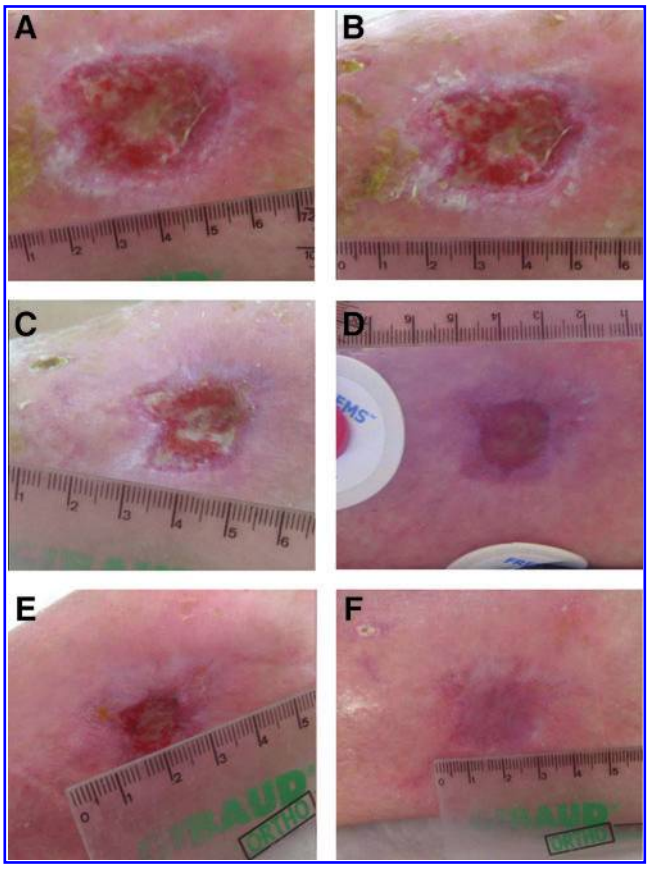

FIG. 2 The figure shows the course of a chronic and painful venous leg ulcer in one older patient treated with frequency rhythmic electrical modulation system (FREMS) and topical treatment with antiseptic (collagenase/chloramphenicol) and hydroalginate at baseline (t0) (**A**), after 5 days of treatment (t1) (**B**), after 10 days of treatment (t2) (**C**), after 15 days of treatment (t3) (**D**), after a follow-up of 15 days (t4) (**E**), and after a follow-up of 30 days (t5) (**F**). Color image is available online at www.liebertpub.com/rej

Electrical wound healing is described in the literature as additional method for the treatment of leg ulcers and wounds.[23,34] One study suggested the effectiveness of FREMS in the treatment of chronic painful leg ulcers in 35 patients with 43 leg ulcers of various etiology (arterial, venous, mixed arterial and venous, and diabetic leg ulcers) that were separated into two random groups, one treated with FREMS and one as control group.[17] In this study, Janković and Binić reported that after 15 treatment sessions (5 days a week for 3 consecutive weeks) lasting 40 min, patients in FREMS group showed a more rapid efficacy in the reduction of pain and epithelization of ulcers.[17] Several authors described the effectiveness of FREMS in the treatment of painful diabetic neuropathies.[11–13] In these studies, in addition to its analgesic effect, FREMS treatment was shown to improve cutaneous blood flow measured by laser doppler flowmetry and partial tissue tension of oxygen and carbonic anhydride by oxymetry[11,13] and also several other functional peripheral nerve parameters, such as electroneurography and vibration perception threshold.[12]

The present study suggested a greater effectiveness of FREMS and topical treatment as compared to topical

Table 2. Differences (t_1-t_0, t_2-t_1, t_3-t_2,t_4-t_3 and t_5-t_4) in All Outcome Measures [Visual Analogic Scale (VAS) and Leg Ulcer Area] in Patients with Painful Venous Leg Ulcers Who Received Frequency Rhythmic Electrical Modulation System (FREMS) Plus Topical Treatment (Group A) or Topical Treatment Alone (Group B)

	Visual Analogic Scale		*Are of leg ulcers (cm^2)*	
	Mean ± SD	p *value*	*Mean ± SD*	p *value*
Group A				
t_0	9.1 ± 1.05		9.11 ± 2.02	
t_1	3.4 ± 1.89	0.005[a]	8.11 ± 2.15	0.005[a]
t_2	2.4 ± 1.26	0.026[a]	6.48 ± 1.89	0.005[a]
t_3	1.6 ± 0.84	0.20	3.85 ± 1.71	0.005[a]
t_4	0.3 ± 0.67	0.12	1.62 ± 0.38	0.007[a]
t_5	0.2 ± 0.42	0.12	1.02 ± 0.31	0.005[a]
Group B				
t_0	9 ± 1.05		9.89 ± 2.02	
t_1	7.8 ± 1.22	0.10	8.94 ± 1.82	0.005[a]
t_2	7 ± 1.63	0.20	8.1 ± 1.37	0.005[a]
t_3	6.6 ± 1.57	0.46	7.46 ± 1.42	0.005[a]
t_4	7.33 ± 1.2	0.005[a]	7.15 ± 0.69	0.407
t_5	4 ± 0.66	0.18	6.9 ± 0.99	0.322

VAS and ulcer's area values are shown as means ± SD. Values after 5 days (t_1), 10 days (t_2), 15 days of administrated treatment (t_3) and after 15 (t_4) and 30 (t_5) days of follow-up were compared with baseline (t_0) in group A and group B.

[a]Statistically significant.

SD, Standard deviation.

treatment alone in patients with chronic and painful venous leg ulcers. In contrast to the Janković and Binić study,[17] we limited our analysis to the types of ulcers that excluded the pathological factors of diabetic neuropathy, as microangiopathy of the vasa nervorum, loss of axons, and axonal atrophy, which are common to all long-term complications of diabetes mellitus. So, it was possible to observe the effectiveness of FREMS on peripheral nervous and vascular systems not altered by diabetes. To best of our knowledge, this is the first study conducted to evaluate the effectiveness of this treatment in only venous leg ulcers in older patients.

In the present study, in the group treated with FREMS and topical treatment, the VAS score showed a statistically significant reduction after only 5 and 10 days of treatment as well as 15 days of treatment and during the follow-up, whereas the patients in the group with topical treatment alone had a reduction of pain score only at 15 days of follow-up. Pain is a frequent experience for patients with leg ulcers, and given that ulcers are often chronic and frequently relapse, they contribute greatly to the burden of pain in elderly patients. Increasing evidence suggests that FREMS treatment may quickly reduce the painful symptomatology of leg ulcers.[12,15,17] This therapeutic modality uses a particular waveform characterized by a sharp spike and an asymmetrical shape (pulse amplitude from 0 to 300 V, frequency 1,000 Hz automatically modulated series having a width from 10 to 40 μsec and intensity from 100 to 170 μA, wherein each pulse has a peak that has a width from 7 to 12 nsec and a voltage up to 220 V increased and adjustable by the patient via remote control in steps of 1 V).[14] The impulse amplitude is preset by the operator using a remote control at the maximum value according to the patient's sensitivity threshold of the stimulated tissue. The system then modulates the maximum amplitude based on the ionic balance of the tissue beneath the electrodes, keeping it in constant equilibrium (biofeedback). The impulse is characterized by an active phase and a rest phase, which ensures ionic balance for the tissue involved in the process.

The action of FREMS developed an analgesic effect on the nerve terminations, whereas there was an evident reduction

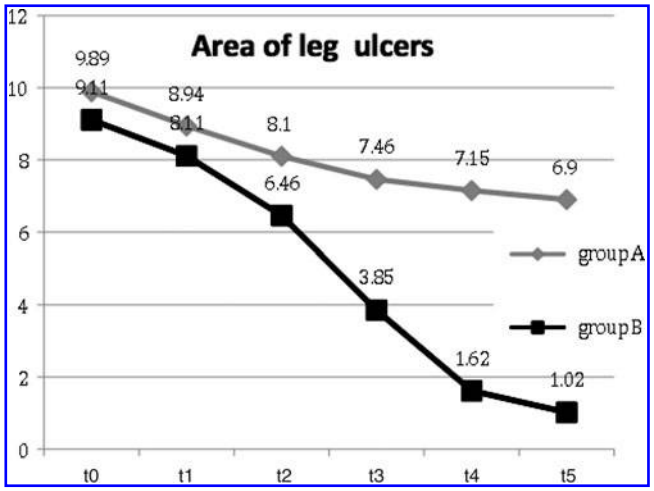

FIG. 3 Decrease of mean area of leg ulcers (cm^2) of chronic and painful venous leg ulcers in older patients treated with frequency rhythmic electrical modulation system (FREMS) plus topical treatment (group A, blue diamonds) or topical treatment alone (group B, red squares). t_0, before treatment; t_1, 5 days after treatment; t_2, 10 days after treatment; t_3, 15 days after treatment; t_4, 15 days of follow-up; t_5, 30 days of follow-up.

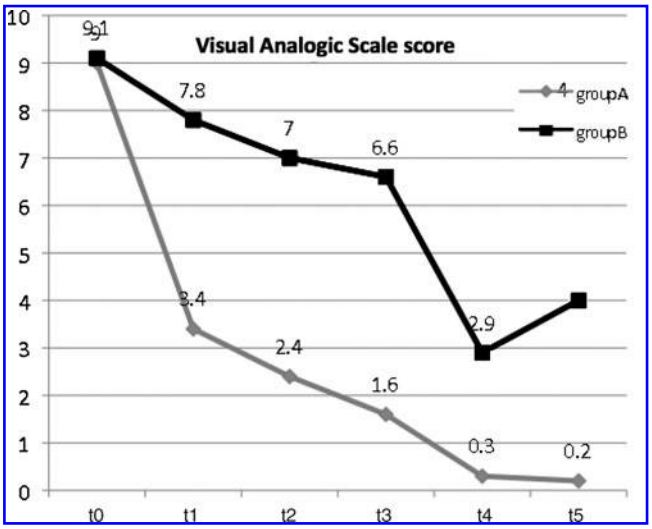

FIG. 4 Decrease of mean Visual Analogic Score (VAS) score in patients with chronic and painful venous leg ulcers treated with frequency rhythmic electrical modulation system (FREMS) plus topical treatment (group A, blue diamonds) or topical treatment alone (group B, red squares). t_0, Before treatment; t_1, 5 days after treatment; t_2, 10 days after treatment; t_3, 15 days after treatment; t_4, 15 days of follow-up; t_5, 30 days of follow-up.

Table 3. Differences at the Baseline, During the Treatment, and Follow-Up for All Outcome Measures (Visual Analogic Scale [VAS] and Leg Ulcer Area) Between Patients with Painful Venous Leg Ulcers Who Received Frequency Rhythmic Electrical Modulation System (FREMS) Plus Topical Treatment (Group A) or Topical Treatment Alone (Group B)

		Group A mean ± SD	*Group B mean ± SD*	*Mann–Whitney test p value*
t_0	Area of leg ulcers (cm^2)	9.11 ± 2.02	9.89 ± 2.02	0.436
	VAS	9.10 ± 1.05	9.00 ± 1.05	0.912
t_1	Area of leg ulcers (cm^2)	8.11 ± 2.15	8.94 ± 1.82	0.353
	VAS	3.40 ± 1.89	7.80 ± 1.22	< 0.005[a]
t_2	Area of leg ulcers (cm^2)	6.40 ± 1.89	8.10 ± 1.37	0.035[a]
	VAS	2.40 ± 1.26	7.00 ± 1.63	< 0.005[a]
t_3	Area of leg ulcers (cm^2)	3.85 ± 1.71	7.46 ± 1.42	< 0.005[a]
	VAS	1.60 ± 0.84	6.60 ± 1.57	< 0.005[a]
t_4	Area of leg ulcers (cm^2)	1.62 ± 0.38	7.15 ± 0.69	< 0.005[a]
	VAS	0.30 ± 0.67	7.33 ± 1.20	< 0.005[a]
t_5	Area of leg ulcers (cm^2)	1.02 ± 0.31	6.90 ± 0.99	< 0.005[a]
	VAS	0.20 ± 0.42	4.00 ± 0.66	< 0.005[a]

t_0, Before treatment; t_1, 5 days after treatment; t_2, 10 days after treatment; t_3, 15 days after treatment; t_4, 15 days of follow-up, t_5, 30 days of follow-up.
[a]Statistically significant.
VAS, Visual Analogic Scale; SD, standard deviation.

of the surface of the ulcer. In fact, this therapeutic modality induces measurable changes in skin microvascular blood flow by proangiogenic effects that increase vascular endothelial growth factor (VEGF) production and release by endothelial cells and require VEGF receptor activation.[16] The epithelization of skin can be explained also by the effect of

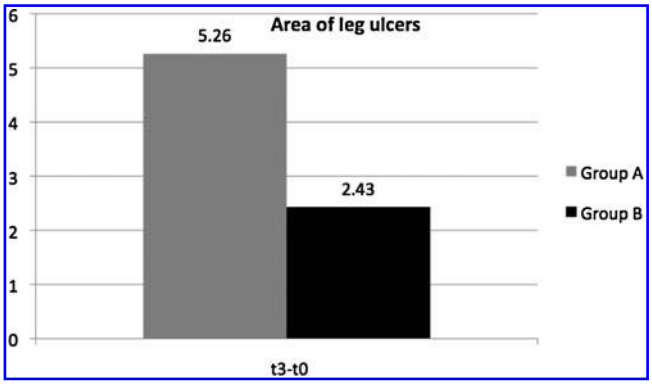

FIG. 5 Change in area of leg ulcers (mean of differences, t3-t0) in patients with chronic and painful venous leg ulcers treated with frequency rhythmic electrical modulation system (FREMS) plus topical treatment (group A, blue) or topical treatment alone (group B, red). t_0, Before treatment; t_1, 5 days after treatment; t_2, 10 days after treatment; t_3 , 15 days after treatment.

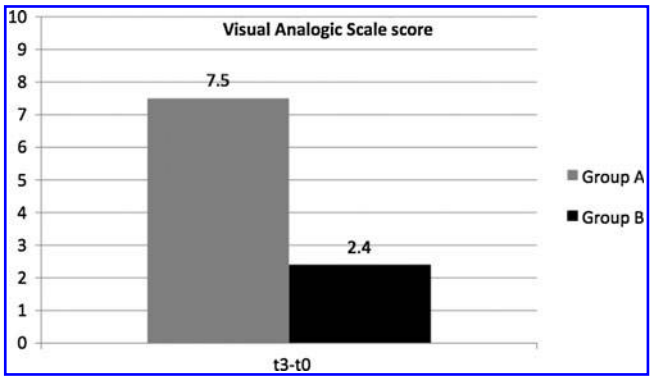

FIG. 6 Change in Visual Analogic Score (VAS) score (mean of differences, t3-t0) in patients with chronic and painful venous leg ulcers treated with frequency rhythmic electrical modulation system (FREMS) plus topical treatment (group A) or topical treatment alone (group B). t_0, Before treatment; t_1, 5 days after treatment; t_2, 10 days after treatment; t_3, 15 days after treatment.

FREMS on cytoskeleton reorganization. Electrical impulse-induced endothelial cell orientation and alignment may also involve actin filament (F-actin) and microtubule rearrangements, because both of these elements reoriented and aligned with the long axis of the cells after exposure to electrical impulses.[16,25] The group treated by topical treatment alone did not show a clinical picture of important improvement. The effectiveness of medical-topical treatment is largely described,[24–28] but in this study, the use of FREMS may have decreased pain thus allowing the topical treatment to be administered more effectively. Furthermore, the improvement of the clinical picture was faster in the FREMS group in comparison with the group receiving topical treatment alone.

The results of this randomized clinical trial demonstrate the therapeutic and analgesic efficacy of FREMS, showing additional beneficial effects of this novel transcutaneous electrotherapy on chronic and painful venous leg ulcers in older patients. Even with these promising findings, limitations to the present study include the lack of long-term follow-up data. Moreover, the lack of a sham therapy in the comparator group receiving topical treatment alone has constrained our ability to claim cause and effect. In particular, this limitation may influence the pain rating scale of the subjects. Furthermore, our protocol including 15 treatment sessions over a period of 3 weeks could be challenging to apply in clinical practice in older patients. Finally, although there is good power estimation in detecting mean differences of VAS of our sample size in both group A and group B, we had a small number of patients in these two groups. Although further studies are needed to confirm the effectiveness of this type of transcutaneous electrotherapy in treating chronic and painful venous leg ulcers in older patients, combined FREMS and topical treatment demonstrated greater beneficial effects in reducing pain and the area of ulcers in comparison with topical treatment alone. The results of the present report are encouraging, but other randomized controlled trials with greater samples, longer-term findings, and possible comparisons with other conservative interventions are needed in the near future.

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Author Disclosure Statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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