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ORIGINAL PAPER

# Frequency rhythmic electrical modulation system in the treatment of chronic painful leg ulcers

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**Abstract** Electrical current has been recommended for use on chronic wounds; however, the ability of this modality to improve healing of various types of chronic ulcers, arterial, venous, mixed arterial and venous ulcers, diabetic, and pressure ulcers is not well established. The purpose of this study was to examine the effect of frequency rhytmic electrical modulation system (FREMS) on healing of chronic painful leg ulcers.

Thirty-five patients with 43 chronic painful leg ulcers participated in the study. The subjects were separated into two random groups, one treated with FREMS and the control group. Our investigation focused on the control of the parameter changes important for ulcer healing: wound surface area, wound appearance (fibrin accumulations, exudation, granulation, and epithelization), ulcer surroundings and associated symptoms. All the parameters were monitored clinically at the beginning, after first, second, and third week, and at the end, after 1 and 2 months of administered therapy, when the scores were determined. Pain intensity was evaluated with visual analog scale (VAS). FREMS therapy was administrated through the device model Aptiva Ballet into sessions and several stages. Comparing the findings of decrease leg ulcer surface, pain, leg ulcer score, score of vicinity (statistically significant at the level $P < 0.05$) with the controls, it was established that FREMS system accelerated ulcer healing, reduced pain and demonstrated better effects compared to the control group. The results of the study indicate that FREMS therapy accelerates wound closure and depresses the pain of chronic leg ulcers.

**Keywords** FREMS · Leg ulcer · Wound · Pain · Epithelization

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## Introduction

Leg ulceration is an important and common health problem and as such is often managed by dermatologists. Chronic leg ulcers due to venous insufficiency, atherosclerosis, diabetes, or small vessel disease are a common chronic disease requiring continuing therapeutic surveillance; they significantly influence the quality of life of the affected due to associated pains, edemas, eczema, superficial purulence, thrombophlebitis, polyneuropathy, etc., [3, 6, 20, 21]. The problem is even greater because one patient may have several causes and this may vary in time. So, a patients with diabetes and patients with a long-standing, pure venous ulcer may have arterial insufficiency developed with increasing age, which adds to the problem and makes the treatment more difficult [20, 29].

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 the elderly patients. Despite the poor treatment of wound pain, there is a growing appreciation of the need for awareness of patient's pain [11, 36, 39].

Also, the applied treatments may be expensive, often without any effects. Standard treatments of leg ulcers comprise mechanical and enzymatic debridement, various types of dressing (alginates, hydrocolloids, hydrogels, dressing with active charcoal and silver, etc.) [6, 30, 31]. Type, localization, and depth of ulcers, amount of necrotic tissue and amount of exudation are the criteria which 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, etc., [13, 24].

Nowadays, extensive investigations are being conducted aiming at finding novel therapeutic methods in leg ulcer treatment.

Several putative therapeutic approaches have been proposed, including the use of antiseptics, antibiotics, growth factors, pressurized oxygen, biologically engineered skin substitutes, and physical therapy modalities such as electrical stimulation and electromagnetic fields [10, 21, 26, 30, 35, 44, 48].

FREMS has recently been developed as a novel electrotherapy. This method is different from other known electrotherapy systems, as it uses sequences of modulated electrical stimuli that vary automatically in terms of pulse frequency and duration. The voltage amplitude is led by patient. The FREMS method was designed on the basis of the hypothesis that the summation of sub-threshold electrical stimuli, conveyed through the skin proximal to a motor nerve in a non-invasive system, would induce composite motor action potentials in excitable tissues. A single impulse of low intensity and short duration, such as that used by conventional electrotherapies, is unable to overcome the dielectric skin barrier to excite the underlying nervous, muscular tissue, and vascular vessels [4, 5, 7, 15, 37].

However, FREMS achieves this effect through specific sequences of weak impulses, characterized by the rapid increase and decrease in pulse frequency and duration, which result in the gradual recruitment of membrane potentials in the stimulated tissues [7, 15, 37].

## Aims

The aim of the study was to establish the effects of FREMS therapy as a novel treatment of painful leg ulcer healing.

## Materials and methods

This is an open, randomized, and controlled study performed in the Department for Peripheral Circulation Diseases and Section for Physical Therapy, Clinic of Dermatovenerology, Clinical Centre of Niš.

The study included 35 patients with various number of leg ulcer and time duration. The patients were randomized into two groups: group of 20 patients with 24 leg ulcers (20 venous, 2 arterio-venous, 1 arterial and 1 diabetic leg ulcer) with FREMS treatment and the control group of 15 patients with 19 leg ulcers (17 venous and 2 arterial-venous leg ulcers). All ulcers in this study were located below the level of the knee. FREMS therapy was administered in patients with chronic leg ulcers, where there was clinical assessment that they need associate treatment. Patients in our study were not previously been treated with electric, magneto, or light therapy.

The clinical signs and ankle-brachial pressure index (ABPI) can be used as a diagnostic method for type of leg ulcer: arterial (ABPI $< 0.8$), venous (ABPI $\geq 0.8$), and mixed arterial and venous ulcers (clinical signs of varicose vein and ABPI $< 0.8$). Hyperglycaemia (blood glucose level higher at 6.3 mmol/l) and clinical diagnosis diabetes mellitus were used for diagnostic diabetic ulcer. Exclusion criteria were patients suffering from a diagnosed neoplastic pathology, patients with a pacemaker, defibrillator, or neurostimulator, patients with renal diseases, malignancies, and patients on chemotherapy, pregnant women and patients with a history of epileptic fits and patients on chemotherapy.

Wound healing and tissue repair which was evaluated clinically required specialized equipment with the VeV MD system as a non-contact technique based on the use of digital image analysis. The Verge Videometer (VeV) is a tool for precise wound measurements, assessment, documentation, tracking, and outcome evaluation. The system calculated the maximum length and width together with the total surface area [47].

Pain intensity was evaluated with the visual analog scale 0–10 (VAS) and pain intensity presented in the numerical scale from 0 = no pain to 10 = worst pain.

The following parameters were controlled: ulcer (number, surface, borders, fibrin deposits, exudation, granulation, and epithelization), ulcer vicinity (erythema, edema, maceration, desquamation, and itch). Epithelization and granulation of the leg ulcers were evaluated on the 0–3 scale (0 prominent, 1 moderate, 2 slight, 3 absent). For evaluation of other parameters such as fibrin deposits, exudation, edema, erythema, maceration, desquamation, and itch the 0–3 scale was also used (0 absent, 1 slight, 2 moderate, 3 prominent). In each check-up of the treatment effect the ulcer score was determined for ulcer 0–12; for ulcer vicinity 0–15.

Surface area of the wound healing epithelization, leg ulcer parameters, and pain evaluated six times: at baseline, at the end of first, second, and third week of treatments, at the end of first and second month after completion of the study.

Appropriate care and dressing of ulcerations were performed every day to both the groups and included non-adherent gauze pads, hydrogels, hydrocolloids, and absorbent foam dressings. Dressings suspected of adversely interacting with electrical stimulation were not prescribed.

A standardized dressing protocol was not used in this study; rather, dressings were tailored to meet the needs of each subject and to promote moist interactive healing. In most cases, the wound dressing used by the patient before enrolling in the study was continued throughout the treatment period. Compression therapy was not administrated in patients with venous leg ulcers.

Utilization of topical treatment to control groups was based on the clinical examine of leg ulcer. Control group ulcers were not treated with FREMS therapy. Pain treatment in the control group was conventional analgesics.

Patients in FREMS group received 15 treatment sessions (5 days a week for three consecutive weeks) lasting 40 min each by the hospital. Slight reddening of the skin was a sign of correct application of FREMS therapy.

FREMS was administrated through the device model Aptiva Ballet (Lorenz Therapy System; Lorenz Biotech, Medolla, Italy), which was equipped with four desynchronized and independent channels with two pair's electrodes [red positive (+) and black negative (−)] and involved the application of an electrical signal through small transcutaneous electrodes. Channel 1 was usually applied to the calf or anterior tibial muscle, [positioning the (+) electrode on the muscle venter and the (−) one on the tendinous muscle insertion]. Channel 2 applied them on a part of healthy and well-cleaned tissue around the leg ulcer. Position of this electrode changed each session for a usual few millimeters from left to the right direction of the leg ulcer surround. Channel 3 applied one under each malleolus ((+) electrode on the internal side of the ankle, (−) electrode on the lateral malleolus) and channel 4 placing the (+) electrode on the back and the (−) one on the sole. FREMS equipment has regulatory standards of CE certificates especially certificates UNI CEI EN ISO 14971 (2004).

"FREMS™" pulses and sequences (patented) its negative square-wave pulses with 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 μs and intensity from 100 to 170 μA, wherein each pulse has a peak that has a width from 7 to 12 ns and a voltage up to 220 V increased and adjustable by the patient via remote control in steps of 1 V). It is composed of sequences of electrical impulses (spikes), with a minimum amount of charge exchange, and a variable frequency and duration according to preset protocols. 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 ensure the ionic balance for the tissue involved in the process.

The one-way repeated ANOVA test for repeated measures was used to analyze changes in all variables in FREMS and control group. The independent samples $t$ test was used to analyze the changes in all variables in two groups. Descriptive statistics are reported as mean ± SD. Comparison of the effects of FREMS with those of control was made using all FREMS and control series.

Data were analyzed using analysis of variance for multiple comparisons (SPSS 10 for Windows), with significance set at $P < 0.05$.

In this study, the protocol used was recommended by manufacturer and guidelines of good clinical practice. The study protocol was approved by the ethics committees of University Clinical center of Nis (Serbia), and written informed consent was obtained from all patients prior to enrolment.

## Results

Detailed characteristics of the demographic information patients and ulcerations are provided in Table 1. The characteristics of the age, ABPI, blood glukose level, and pain assignment groups were not significantly different at baseline. Sex and duration of the leg ulcers presented as significant different ($P < 0.01$). The relatively higher mean value of duration in the control group was due to two subjects in this group who had ulcers that had been present for 5.7 and 6.3 years.

Within-treatment analysis showed that, following FREMS treatment, there was a significant decrease in surface leg ulcer, pain score, score of ulcer, and ulcer vicinity ($P < 0.05$). Ulcer vicinity in the FREMS group was not significant in the second month. VAS score decreased in all control measurements and was significant ($P < 0.001$).

**Table 1** Baseline patient characteristics

| Characteristic | FREMS ($n = 20/24$) | Control ($n = 15/19$) | $P$ value |
|---|---|---|---|
| Sex | 1.70 ± 0.47 | 1.86 ± 0.35 | $P < 0.01$ |
| Age (years) | 66.70 ± 4.46 | 70.47 ± 9.22 | NS |
| Duration | 10.50 ± 1.41 | 11.74 ± 2.47 | $P < 0.01$ |
| Ankle-brachial index | 82.90 ± 5.3 | 81.86 ± 6.30 | NS |
| Blood glucose level (mmol) | 5.59 ± 2.24 | 5.38 ± 0.53 | NS |
| Visual analog scale (mm) | 7.84 ± 1.70 | 7.47 ± 1.61 | NS |
| *Type of ulcer* | | | |
| Venous | 20 | 17 | |
| Arterial | 1 | – | |
| Mixed | 2 | 2 | |
| Diabetic | 1 | – | |

Within-treatment analysis in control group, showed statistically significant decrease leg ulcer surface and ulcer score in the third week and first month ($P < 0.05$). Decrease score for ulcer vicinity is statistically significant in the first week ($P < 0.02$), the second week ($P < 0.01$), and the third week ($P < 0.05$). VAS score decreased without significance in the control group.

When compared results of the FREMS and control group, decrease surface of the leg ulcer was significant in control measurements in the third week ($P < 0.003$) at the end of first and second month ($P < 0.001$) (Fig. 1). Decrease ulcer score was correlated with decrease leg ulcer surface in control measurements in the third week ($P < 0.006$), at the end of 1st and 2nd month ($p < 0.001$). Ulcer vicinity was significant in measurements at the end of the second week ($P < 0.05$), third week ($P < 0.04$) and after first month ($P < 0.02$). Pain decrease was statistically significant in the all control measurements ($P < 0.001$). Decrease VAS pain score after 2 month presented in Fig. 2.

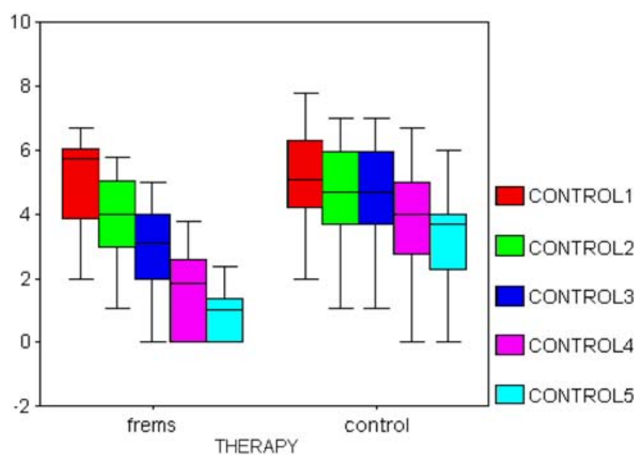


**Fig. 1** Decrease of mean surface leg ulcer FREMS and control

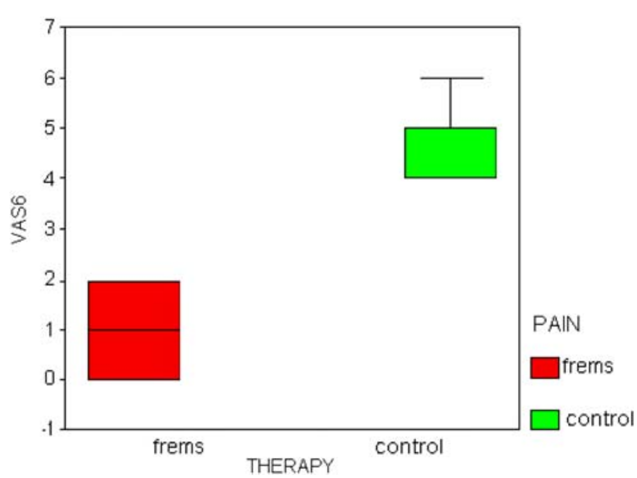


**Fig. 2** Decrease of mean VAS score FREMS and control at the end of treatment

Characteristic value at the baseline and at the end of study in the FREMS and control is presented in Table 2.

No systemic side effects were recorded during the study. Patients reported only a very slight burning sensation at the site of electrode placement during the series of treatments later revealed as FREMS, with no residual skin signs. Tissue repair and epithelization during FREMS therapy presented in the Fig. 3a (baseline), b (after 2 week treatment), c (after 3 week treatment), and d (after 1 month at the end of treatment).

## Discussion

Dermatologist through scientific work significantly contributes not only to the understanding of pathophysiology of healing, but also to the improvement of general principles of treatment of chronic painful leg ulcers of various etiologies [8, 9, 17, 38]. Therapy of tissue repair and pain of leg ulcer and wounds generally based on various topical modalities and analgesic drugs, but the frequency of side effects and the lack of efficacy of these agents in a significant proportion of cases has spurred the search for non-pharmacological treatments [11, 31, 42].

Electrical wound healing is described in the literature as additional method for the treatment of leg ulcer and wound [7, 14, 19, 31, 33]. When discussing electrical stimulation, it is important to distinguish the waveform used for the protocol. Although there are two basic types of currents, which include direct current (DC, referred to as galvanic current-unidirectional flow) and alternating current (AC, reffered to as continuous bidirectional flow which waveform represented by one cycle), a third type is pulsed current (PC, referred to as brief unidirectional or bidirectional flow of electrons or ions which each pulse described by its waveform, amplitude, duration, and frequency) [13, 32].

However, there are many waveforms available on electrotherapy equipment. Wolcott et al. [48] used microampere DC to treat venous leg ulcers on 15 patients. They reported that after 6 weeks of daily ES treatment that totaled 6 h, the mean healing rate per week was 14.4%, which resulted in a mean volume reduction of 85%. Junger et al. [27] showed the effect of electrical stimulation (ES) on wound healing and angiogenesis when treated 15 venous leg ulcers in 38 days with daily ES for 30 min when the mean ulcer area decreased 63%. Franek et al. [16] treated 33 patients with high-voltage PC and showed significant decrease in wound size for 7 week treatment. Houghton et al. [23] treated 42 chronic leg ulcers (diabetic, venous, and arterial) with high-voltage PC for 4 weeks and followed up 1 month and showed significant difference in wound size. Alon et al. [1] used high-voltage PC to treat 15 neuropathic diabetic foot ulcers and reported that 12

**Table 2** Effect of treatment with FREMS or control

| | FREMS | | Control | | P value |
|---|---|---|---|---|---|
| | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment | |
| Surface of leg ulcer | 6.18 ± 1.72 | 1.13 ± 1.58 | 5.91 ± 1.16 | 3.17 ± 1.83 | $P < 0.001$ |
| Score ulcer | 10.50 ± 1.23 | 0.25 ± 0.55 | 10.68 ± 1.10 | 3.52 ± 1.50 | $P < 0.001$ |
| Vicinity | 11.85 ± 1.92 | 1.15 ± 1.13 | 11.66 ± 2.25 | 1.66 ± 1.34 | NS |
| VAS | 7.84 ± 1.70 | 1.68 ± 1.63 | 7.47 ± 1.61 | 5.21 ± 1.18 | $P < 0.001$ |


**Fig. 3** **a** Leg ulcer appearance before FREMS treatment. **b** Decrease leg ulcer surface after 2 week treatment. **c** Decrease leg ulcer surface after 3 week treatment. **d** Complete wound closure after 1 month

wounds (80%) healed completely in a mean period of 2.6 months. Lundeberg et al. [34] evaluated the effect of biphasic asymmetric PC on wound healing of 64 patients with chronic diabetic neuropathic foot ulcers. After 12 weeks, there was a statistically significant treatment effect based on the closure of 42% of wounds. Debreceni et al. [14] reported results of treating 24 individuals (10 diabetic) with chronic ischemia, 12 of which had ischemic ulceration and six distal gangrene with preogressive deterioration of their ischemic lower limbs with biphasic symmetrical PC over a period of 1 year. Therapy results showed significant healing progres, including diasappearance of ischaemic pain.

Similar efects of electrical wound healing were in studies which included wounds related to nonischemic diabetic neuropathy and diabetic ischemic wounds [1, 2, 7, 18, 25, 40, 41, 46]. In general, the duration of treatment varied between studies, often depending on the size of the initial ulcer and the rate of healing [23, 32]. In the majority of clinical trials, electrical stimulation was given three times per week until the chronic ulcer healed [12, 13, 32]. There was no direct evidence to determine the optimal duration or amount of electrical stimulation. However, it would be clinically rational and appropriate to discontinue treatment with electrical stimulation if the ulcer is not healing. Consistent with Agency for Health Care Research and Quality guidelines on treatment of pressure ulcers, a chronic wound should demonstrate progressive healing within 4 weeks if the used treatment is effective [32, 43].

There was insufficient evidence to determine the best type of device and most effective form of electrical stimulation for treatment of chronic wounds or ulcers. There appears to be no standard type, waveform or frequency of electrical stimulation and suggests that the various type of electrical stimulation may have a similar, but not identical mechanism of action at tissue and neuro-muscular level [13, 23, 32].

Indeed, FREMS therapy is based on changes in frequency and duration of electrical impulses emitted by an electrical stimulator.

We have demonstrated that FREMS is a safe and effective therapy for tissue repair and surrounding of painfull leg ulcer of various etiology.

Significant differences on the baseline with sex and duration of leg ulcers can be explained by random choice of patients who attended clinic in this period. At the end of FREMS sessions, we observed a significant reduction of leg ulcer surface (−86.7%), score of ulcer (−92.10%), ulcer vicinity (−87.62%) and pain (−80.9%). This non-invasive treatment was demonstrated to be safe and was not associated with any side effects [7, 15, 37]. This finding could be specific to FREMS, since none of the non-pharmacological treatments for painful leg ulcer investigated to date have reported a beneficial effect lasting for more than a few weeks. The mechanism of action of FREMS in the tissue repair was not investigated in this study, and can therefore only be speculated upon. Based on a number of assumptions, an attractive hypothesis is that FREMS stimulates the release of angio genetic growth factors, activate a functional "rehabilitation" mechanism which results in an functional reactivation of degenerated biological tissue due to metabolic decompensation, deactivation of symptomatic neuro-muscular feedback processes, mobilization of inflammatory and pro-inflammatory factors and acceleration in the repair of damaged tissue [7, 15, 37]. The application of FREM electrodes to the skin during therapy is followed by a long-lasting anesthesia–analgesia effect [7]. Alternatively, FREMS therapy and pain effect hypothesised simply reflect some functional changes of the nerve; structural changes may only occur at a later stage, possibly providing the basis for the long-term effects of this therapy. Subjects wich enrolled in our study were affected by relatively severe pain, which is normally associated with leg ulcer and tissue damage [7, 15]. Nonetheless, studies on experimental models are needed in order to clarify the mechanisms that underlie the effects of FREMS.

Indirect findings that may be related to the effects of FREMS include: the induction of the synthesis of vascular endothelial growth factor (VEGF) and other angiogenic factors and angiogenesis promotion by different electrical [4, 5, 22, 28] or electromagnetic [45] stimuli; increased nerve conduction velocity after an improvement in blood flow in the lower limbs, achieved through either revascularisation [49, 50].

The results of this clinical study demonstrate the therapeutic and analgesic efficacy of FREMS, and show additional beneficial effects of this novel electrotherapy on painful leg ulcer electrotherapy. If confirmed in a larger series of cases, and possibly in a multicentre study, these findings may offer new perspectives for the treatment of painful leg ulcer and wound.

Achieved clinical results in the improvement of general clinical stage of tissue repair, ulcers surrounding and the pain decreasing represent the effect of tissue repair and biologically active neuromodulation of damaged tissue.

## Conclusion

Frequency rhytmic electrical modulation system significantly facilitates the epithelization of ulcus cruris and significantly decreases the pain level, especially in the first 36–48 h without damaging effects. It has cumulative effect which is evidenced 2 months after treatment. The therapy is comfortable and enables simultaneous treatment of both extremities and is automated by software. Due to the fact that the results of this small clinical research are very good, FREMS therapy can be recommended for the treatment of chronic and especially painful leg ulceration of various etiology.

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