Electrical stimulation as adjuvant treatment for chronic leg ulcers of different aetiology: an RCT

● **Objective:** To investigate the effectiveness of an innovative electrical stimulation (ES) therapy as adjuvant treatment for chronic wounds of various aetiology, in terms of pain and ulcer healing.

● **Method:** Patients with chronic limb ulcers were enrolled for the study and randomised into the intervention or control group. The intervention group received conventional treatment plus ES therapy (FREMS; Lorenz Lifetech) while the control group received only conventional treatment. Each ES treatment cycle consisted of 12 sessions performed in 4 weeks (three sessions/week). All patients were treated until full wound healing occurred, or for a maximum of 9 ES cycles, with a 2-week rest between each cycle.

● **Results:** A total of 60 patients were enrolled in the study and randomised into the two groups: the intervention group (n=30) and the control group (n=30). During follow-up, some patients terminated the protocol because they reached the ulcer closure before the maximum of 9 cycles. The analysis of the effect of ES on pain and ulcer healing was performed on all patients who underwent at least two consecutive clinical evaluations (two cycles), in order to reach a compatible sample size with the primary objective (one patient withdrew). In both groups, there was a significant reduction of pain compared with baseline (p < 0.05), starting from T_6 visit in the first cycle. In particular, there was a significant reduction of pain in the intervention group compared with the control group after 14 days, and this reduction continued until the end of the second cycle. Similarly, there was a significant reduction of PUSH tool score in the intervention group compared with the control group after 14 days, and this reduction continued until the end of the second cycle.

● **Conclusion:** Data collected in this study support data in the literature. Analysis of longitudinal data analysed by simple models and complex models suggest that the ES therapy had a positive and significant effect on pain reduction (VAS) and on the improvement of ulcer healing process in terms of the PUSH tool total index compared with conventional treatment, and may have induced a significant acceleration of the wound-healing process.

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chronic wounds; electrical stimulation; pain; epithelialisation

Various electrical stimulation (ES) methodologies, in terms of electric physical characteristics and application modalities, have been proposed to facilitate wound healing. ES procedures involve application of a low-level electrical current to the wound bed or to the peri-wound using conductive electrodes.[1] These include direct current (DC), alternating current (AC), high-voltage pulsed current (HVPC) and transcutaneous electrical nerve stimulation (TENS). Although the precise mechanisms of action have yet to be completely explained, clinical outcomes have demonstrated some efficacy.[2]

In a systematic review,[3] Cullum et al. showed that there was no clear evidence of a benefit for ultrasound or electromagnetic therapy in the treatment of venous leg ulcers, although they suggested there may be some benefit associated with electrotherapy in the healing of chronic wounds. This suggestion was made with caution, as there are only three small trials published, with a total of 63 patients involved, making it impossible to determine clinically important effects.[3] Furthermore, an unpublished meta-analysis of 17 randomised controlled trials (RCTs) showed that ES was effective in treating chronic wounds (p<0.0001);[4] this analysis also included three RCTs with patients with diabetic foot ulcers (level of evidence=1a).[5]

It has been suggested that ES can help promote ulcer healing through antibacterial effects, and stimulation of growth factors and collagen synthesis.[6,7] As a result, it has recently been included among the treatments recommended for chronic skin ulcers.[8] The recommendation specifies the application modalities, but there are no indications on the electrical signal in terms of energy, frequency and modulation.

C. Magnoni,[1] MD, PhD;
E. Rossi,[1] MD;
C. Fiorentini,[1] MD;
A. Baggio,[1] MD, PhD;
B. Ferrari,[1] MD;
G. Alberto, MD, PhD;
1 University of Modena and Reggio Emilia, Department of Dermatology, Modena, Italy.
Email: cristina.magnoni@ unimore.it

Frequency, Rhythmic Electrical Modulation System (FREMS)

One innovative ES therapy is the Frequency, Rhythmic Electrical Modulation System (FREMS; Lorenz Lifetech), which uses sequences of electrical stimuli that are modulated in terms of duration, pulse frequency and voltage amplitude.

FREMS is a biocompatible, transcutaneous electrical nerve stimulation, with output voltage by means of electrodes with reduced contact surface (~1cm²). It consists of a series of impulse sequences that vary in frequency (1–1000Hz) and duration (10–40µsec). Pulse amplitude is fixed by the operator, according to the sensitivity threshold of the patient, using a remote control. The impulse (spike) is characterised by an active phase (initial phase), which carries the desired action, and by a recovery phase for the ion balance of the tissue.

The FREMS method was designed on the basis of the hypothesis that the summation of subthreshold 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 through specific sequences of weak impulses, characterised by a rapid increase and decrease in pulse frequency and duration. This results in the gradual recruitment of membrane potential in the stimulated tissues.

This stimulation produces a significant enhancement in skin microvascular blood flow with significant effects on perfusion and oxygenation of the treated tissues.[9] Different studies suggest the efficacy of FREMS therapy in the rehabilitation setting for the treatment of pain, especially in patients with diabetes mellitus.[9–11] However, there are only two studies suggesting a role for FREMS in treating chronic leg ulcers.[12,13]

The primary objective of this study was to assess the effectiveness of the ES treatment in patients with chronic leg ulcers in terms of improvement of wound healing and control of pain.

Method

This study was a post-marketing, randomised controlled clinical trial with parallel groups.

Study population

All adult patients (≥18 years), attending a complex wound clinic, with an ulcer on the lower limb of at least 6 months' duration were eligible for inclusion. The catchment area for the hospital-based clinic covered the province of Modena. Patients with diagnosed neoplastic pathology and those with a pacemaker, defibrillator or neurostimulator were excluded from participating. Other exclusion criteria were:
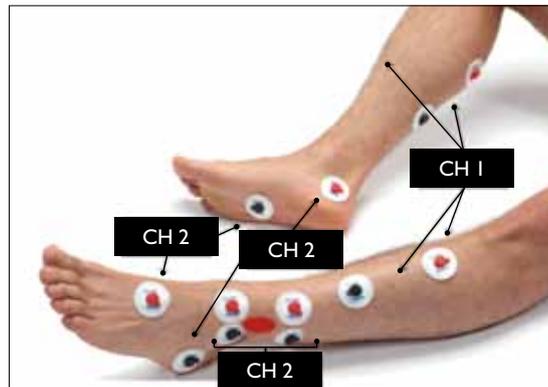- Malignancies
- Patients on chemotherapy
- Pregnant women

Fig 1. Figure to show application of ES device to patient; CH=channel

- Patients with a history of epileptic fits.

The following clinical tests were also performed: blood count, erythrocyte sedimentation rate (ESR), rheumatoid arthritis (RA) test, blood test (PCR), serum iron, total bilirubin and fractional cholesterol, triglycerides, blood glucose, blood urea nitrogen, protein electrophoresis, liver-function test (SGOT and SGPT), alkaline phosphatase, prothrombin time, combined HCV+HIV+AU antigen, C3, C4, cryoglobulins, ANF, IC, complete urine examination, and ecocolour-Doppler.

Treatment protocol

ES treatment was provided in consecutive cycles. Each cycle lasted 4 weeks, with ES treatment three times per week, for a total of 12 sessions, followed by a 2-week rest period. ES treatment cycles were repeated until full healing (complete epithelialisation) or for a maximum of nine cycles, corresponding to a 52-week study period.
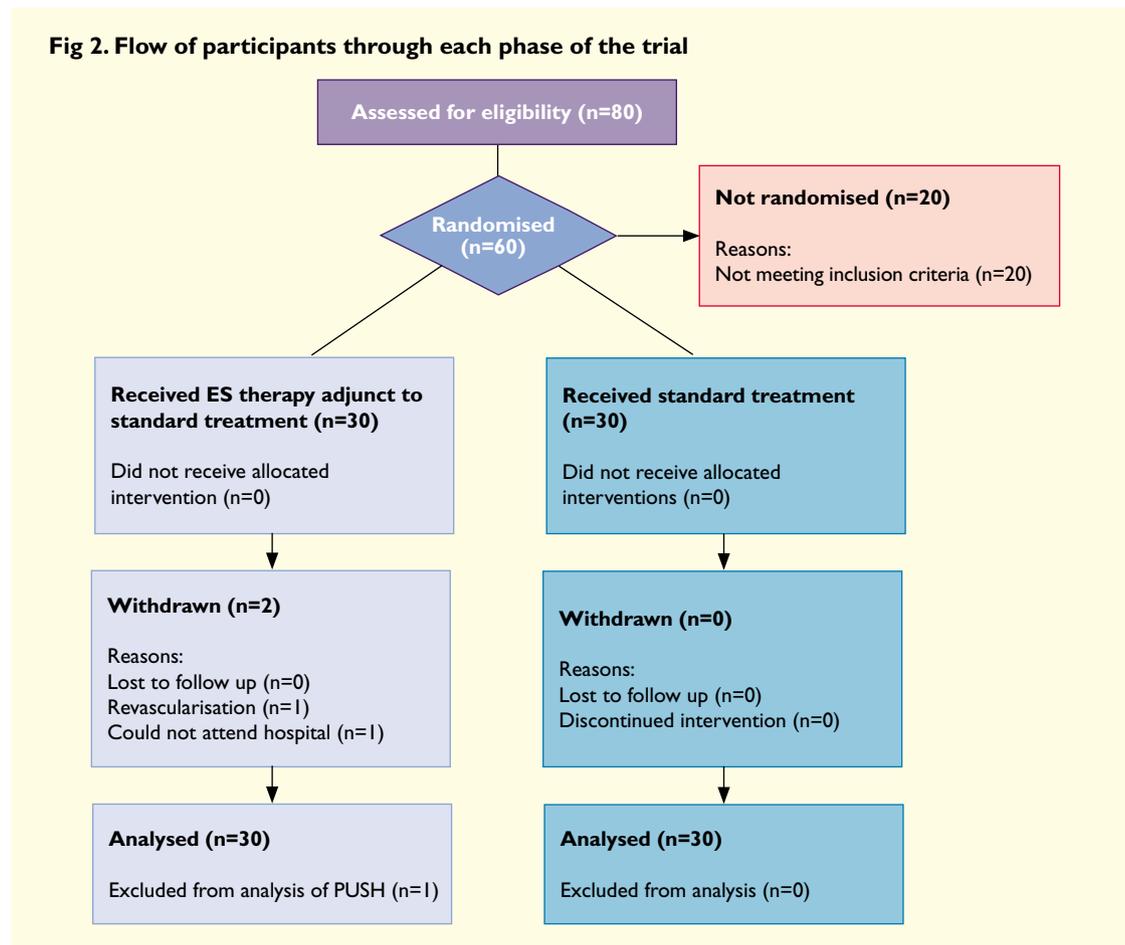
Both groups received the appropriate care and dressing for ulcerations three times a week (conventional care). This included dressings (foam, calcium alginates, hydrogels, hydrocolloids and adhesive membranes) that met the needs of each patient to promote wound healing.

Interventions

ES treatment was delivered through the FREMS medical device Aptiva Ballet (Lorenz Lifetech), which has four desynchronised, independent channels. Each channel has four couples of electrodes, with both a red, positive pole (+) and black negative pole (–). The application of ES through the skin is possible owing to small transcutaneous electrodes.

The Aptiva device has certificate following the European directive 93/42 EEC. FREMS is a biphasic, asymmetric and electrically-balanced pulse, characterised by an active phase with negative voltage spike (–300V) and short duration (10–100µsec), and by a recharging phase with low voltage and long duration (0.9–999msec). Each FREMS treatment is composed of sequences of basic pulses characterised by different features in terms of frequency, amplitude and spike duration (multi-parametric modula-

Fig 2. Flow of participants through each phase of the trial

Assessed for eligibility (n=80)

Randomised (n=60)

Not randomised (n=20)

Reasons:
Not meeting inclusion criteria (n=20)

Received ES therapy adjunct to standard treatment (n=30)

Did not receive allocated intervention (n=0)

Withdrawn (n=2)

Reasons:
Lost to follow up (n=0)
Revascularisation (n=1)
Could not attend hospital (n=1)

Analysed (n=30)

Excluded from analysis of PUSH (n=1)

Received standard treatment (n=30)

Did not receive allocated interventions (n=0)

Withdrawn (n=0)

Reasons:
Lost to follow up (n=0)
Discontinued intervention (n=0)

Analysed (n=30)

Excluded from analysis (n=0)

tion). The specific design of the FREMS pulse (short, high-intensity spike together with long, low recharge) is effective without being harmful. Pulses are electrically balanced in order to avoid burns and electrolyte impairment, and the treatment signal is non-periodic (perceived as stochastic), in order to avoid nerve adaptation.

Treatment time exceeds 20 minutes per session, in order to reach the release of endogenous substances. The impulse amplitude is fixed by the operator, using a remote control at the maximum value, according to the patient's sensitivity threshold of the stimulated tissue. The therapy must be performed by trained health professionals.

During treatment, channel 1 was applied on the calf and anterior tibial muscle, positioning the red electrode proximally and black one distally. Channel 2 was applied on a part of healthy and well-cleaned tissue around the ulcer. Channel 3 was applied under each malleolus (positive electrode on the internal side of the ankle, negative electrode on the lateral malleolus) and channel 4 was placed on the foot, with the red electrode on the back and the black one on the sole (Fig 1).

In this study, each patient in the intervention group received the treatment labelled 'ulcers', which is dedicated to chronic leg ulcers. Each session of the treatment lasted about 35 minutes and included two discrete phases.

Outcomes
All patients from intervention and control groups were examined and monitored during the study period at T_0 (study admission, before the first treatment of cycle one), at T_1 (before the first treatment of the following cycle), at T_6 (before the sixth session of each treatment cycle), at T_{12} (before the twelfth of each treatment cycle) and at T_{end} (at the exit from the study).

All enrolled patients were evaluated in terms of ulcer stage on the basis of the PUSH tool, which is based on observation and measurement of the ulcer and categorisation of the ulcer with respect to surface area, exudate, and type of wound tissue. A sub-score is recorded for each of these ulcer characteristics, with the sub-scores added to obtain the total score.[14] A comparison of PUSH scores measured over time provides an indication of the improvement or deterioration in ulcer healing.[14] Swab samples were also taken, as appropriate, to determine pathogens

responsible for any local wound infection

Pain intensity was evaluated using a patient self-reported 0–10mm visual analog scale (VAS) using a 10-point Likert scale, where 0 = no pain and 10 = worst pain imaginable.

It was not possible to blind the patient or investigator to the treatment, but all patients were followed by the same investigator.

Sample size

A χ^2 model was applied to determine the sample size for the study, as described by Michael Campbell, Medical Statistics, needed to assess the primary outcome measure (proportion of patients who achieved full healing). Analysis of the literature suggested a placebo effect on the control group of 20%, while in the group receiving stimulation, based on a previous pilot study,[12] the effect in active group was estimated as 58%. For a test size of 5% and a statistical power of 90%, the model gave a sample size for each group equal to 29.3 actual patients.

Randomisation

Considering the number of patients and their characteristics, a simple method for randomisation was used, which was managed by the central office located at the sponsor company. A randomisation tool was used to generate the treatment allocation (www.random.org). This yielded a list with the patient allocations to the two groups, which was then placed in a sealed envelope stored in the 'sponsor office'. The investigator was informed of the allocation, by telephone, on a patient-by-patient basis. Patients were randomised to receive either ES treatment with FREMS or conventional treatment, as described above.

Ethics

The study was conducted according to ICH-GCP guidelines and according to the revised Declaration of Helsinki. Each patient gave written, informed consent to participate in the trial, which was approved by the ethics committee of Reggio Emilia and Modena University.

The duration of the study was initially fixed as 12 months, but it was necessary to submit an amendment to the ethics committee to request an additional 6 months, due to a delay in the enrolment of patients.
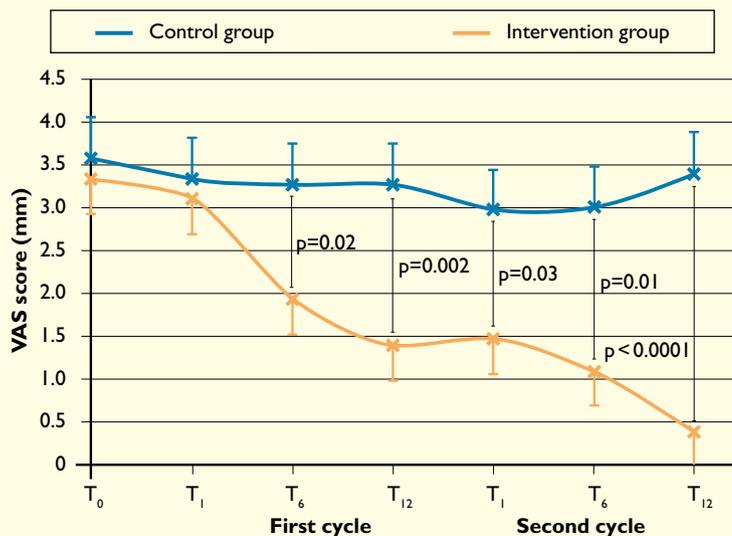
Statistical analysis

Preliminary statistical analysis were used to test the hypothesis of normal distribution of data, with Gaussian approximation. Mean values and standard deviations were calculated for continuous variables, and Student's t-test was applied to compare the two groups at baseline. One-way analysis of variance (ANOVA) tests and Newman–Keuls Post Test for pairing were used to evaluate all the parameters, assuming a normal distribution of data. Results of $p < 0.05$ were considered significant.

Generalised, linear mixed-effects models were applied to study the trend over time for longitudinal data in the two groups and to test the differences, adjusting for the effect of covariates. In detail,

Table 1. Patient characteristics at baseline

	Control group	Intervention group	p-value*
Sex (female/male)	20/10	22/8	0.779
Age (years)	65.1 ± 17.6	65.9 ± 18.4	0.800
Ulcer duration (months)	3.8 ± 6.9	1.6 ± 2.1	0.102
Pain (mm)	3.6 ± 2.9	3.3 ± 2.3	0.736
Length × width (PUSH)	7.1 ± 4.2	5.6 ± 2.8	0.143
Exudate (PUSH)	1.6 ± 1.0	1.3 ± 0.6	0.082
Type of tissue (PUSH)	2.4 ± 0.7	2.4 ± 0.6	0.933
Total PUSH score	**11.1 ± 5.0**	**9.2 ± 2.9**	**0.106**
Infection (n)	11	4	—
Ulcer aetiology			
● Traumatic ulcer	2	0	0.492
● Arterial ulcer	16	13	0.606
● Mixed ulcer	6	14	0.054
● Diabetic ulcer	3	3	1
● Undefined	2	0	0.492
● After burn	1	0	1

* p-values < 0.05 considered significant

Fig 3. VAS values during the first two cycles of treatment

Fig 4. Total PUSH score during the first two cycles of treatment
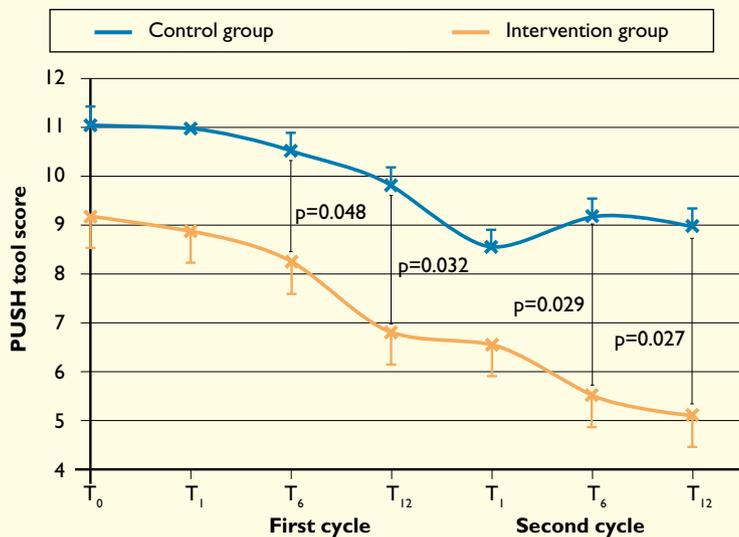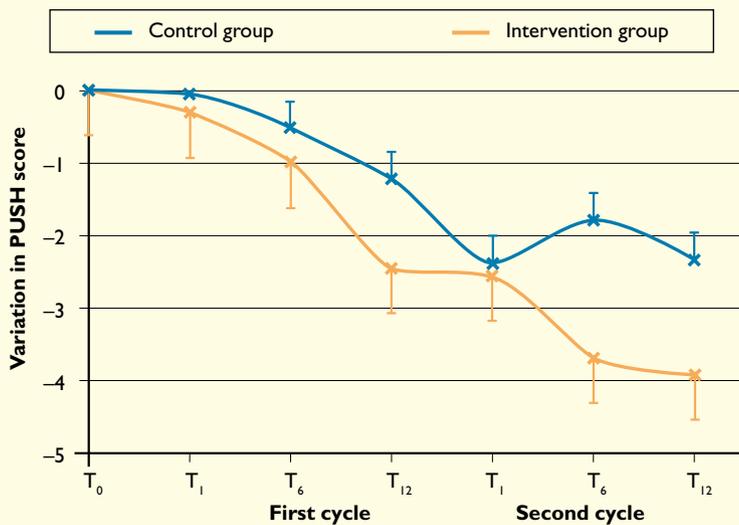

Fig 5. Mean variation in PUSH score

the analysis used model complexes in order to estimate the difference in the trends of variable's variation over time, taking into consideration the effects of covariates. The investigated variables were the VAS pain score and PUSH score.

For each variable, an optimal model was composed in order to consider both the effect of treatment over time and the correspondent value of the covariates. The covariates considered in the model were:
- Type of wound (vascular as a reference, mixed aetiology ulcer, not defined, post skin burn, traumatic or diabetic foot ulcer)
- Age of the ulcer
- Presence of infection.

Results

A total of 60 patients were enrolled into the study and randomised into the two groups: the intervention group (n=30) and the control group (conventional treatment) (n=30). No significant differences were observed between the two groups of patients at baseline (Table 1).

During the follow-up phase, some patients discontinued treatment before the maximum of 9 cycles, due to achieving full healing. Four patients in the control group and six in the intervention group withdrew after the first cycle; five controls and 10 in the intervention group withdrew after the second cycle; 11 controls and nine in the intervention group withdrew after the third cycle; and five controls and two in the intervention group withdrew after the fourth cycle. For the following cycles, two patients in the control group and none in the intervention group withdrew. Only two patients withdrew from the study before achieving full healing (Fig 2).

All patients who had at least two consecutive clinical evaluations were included in the analysis of the effect on pain and PUSH score. To determine the effectiveness of treatment in terms of healing, all subjects were included in the analysis.

Pain

Pain value was assessed by VAS, during all follow-up visits. The longitudinal analysis of VAS data was performed on mean values of VAS absolute numbers. For this analysis the data available until the end of the second cycle were used, in order to have a sufficient number of data to analyse. Twenty-five patients (nine controls, 16 intervention) discontinued treatment after the second cycle because their ulcers had completely healed. Fig 3 shows the mean values of pain (with standard error bar), calculated at each scheduled visit in the two study groups.

In both groups, there was a significant reduction of pain compared with baseline (paired Student t-test, $p<0.05$), starting from T_6 visit in the first cycle. In particular, there was a significant reduction of pain in the intervention group compared with the control group after 14 days, and this reduction continued until the end of the second cycle.

PUSH score

The PUSH tool score was evaluated in total. As with the VAS, the longitudinal analysis was limited to the end of the second cycle. Fig 4 shows the mean values of the parameter, analysed for the two groups at each scheduled visit.

Although the ES group showed a slightly lower value than the control group at the beginning, this was not significant. Both groups showed a significant reduction in PUSH score compared with baseline (paired Student's t-test, $p<0.05$) starting at T_6

visit from the first cycle. There was a significant reduction of PUSH tool score in the intervention group compared with the control group after 14 days, and this reduction continued until the end of the second cycle. The diagram of the mean variations over time of PUSH tool score from baseline clearly shows the trend in the two groups (Fig 5). Single parameters of PUSH tool did not show major effects if analysed separately.

Data modelling
The data collected during the study were also analysed with the complex model. This model studied the trend over time of two variables, pain (VAS) and PUSH tool (size of the lesion, quantity of exudate and type of wound tissue) in the ES and control groups, taking into account the influence of some covariates. The covariates considered in the model were:
- Wound aetiology (vascular, mixed aetiology ulcer, not defined, post-skin burn, traumatic or diabetic foot ulcer)
- Age of the lesion
- Presence of infection.

In this way, it was possible to identify differences between the two groups during the follow-up adjusted for covariates. For each variable, an optimal model was constructed, which took into account both the time elapsed since the beginning of the study at any evaluation of the parameter and the corresponding value of the covariates. The results of the models are reported in Tables 2 and 3 for VAS and PUSH score parameters, respectively.

Generalised, linear mixed-effects models, applied to VAS and corrected for covariates, indicated that at baseline there were no differences between the two groups and a nonsignificant–significant decrease of VAS values in both groups was observed over time. In the ES group, a significant tendency to decrease over time was observed with respect to the reference control group (p=0.007). VAS values increased significantly in presence of infection, while the type of lesion also statistically affected the model; in particular, post-skin burn ulcers (p<0.0001) and undefined ulcer type (p<0.0001) were associated with an increased value of VAS, while traumatic ulcers (p<0.0001) and diabetic foot ulcers (p=0.002) were associated to a diminished value of VAS compared with vascular ulcers.

Generalised linear mixed-effects models applied to PUSH tool and corrected for covariates suggested a statistically significant decrease of PUSH tool parameter over time in both groups (p<0.0001), but in the ES group, a statistically-significant decrease was observed with respect to reference control group (p=0.016). The wound duration (p=0.045) and the presence of infection (p=0.029) were positively associated with the PUSH tool parameter. Traumatic ulcers were associated with a decreased

PUSH score compared with vascular ulcers (p=0.0001), while undefined ulcer type was associated to a significant increase in PUSH score compared with vascular ulcers (p=0.001).

Ulcer healing
At the end of each cycle of therapy the percentage of healed patients was calculated in both groups (Fig 6). The percentage to achieve healing in the intervention group was higher than the control

Table 2. Complex model result for VAS parameter

Covariate	Coefficient	SEM	z	p-value	95% CI
Group at baseline	0.09	0.63	0.14	0.890	−1.14; 1.31
Time	−0.03	0.02	−1.48	0.139	−0.07; 0.01
Group*time	−0.08	0.03	−2.68	0.007	−0.14; −0.02
Ulcer aetiology[†]					
● Mixed ulcer	−0.15	0.43	−0.36	0.720	−0.99; 0.68
● Undefined ulcer	2.36	0.39	5.98	0.0001	1.58; 3.13
● Post-burn ulcer	2.14	0.38	5.70	0.0001	1.40; 2.88
● Traumatic ulcer	−2.70	0.60	−4.49	0.0001	−3.87; −1,.52
● Diabetic ulcer	−1.20	0.39	−3.10	0.002	−1.95; −0.44
Ulcer age	−0.03	0.02	−1.30	0.194	−0.08; 0.02
Infection	0.66	0.20	3.32	0.001	0.27; 1.06
Constant	3.21	0.57	5.62	0.0001	2.09; 4.33

SEM=standard error of mean; 95% CI=95% confidence interval;
† Vascular ulcers were used as a comparison

Table 3. Complex model result for total PUSH tool score

Covariate	Coefficient	SEM	z	p-value	95% CI
Group at baseline	0.18	1.16	0.15	0.879	−2.10; 2.45
Time	−0.14	0.03	−4.24	0.0001	−0.20; −0.08
Group*time	−0.14	0.06	−2.41	0.016	−0.25; −0.03
Ulcer aetiology[†]					
● Mixed ulcer	−1.57	1.14	−1.38	0.169	−3.81; 0.67
● Undefined ulcer	2.91	0.91	3.19	0.001	1.12; 4.70
● Post-burn ulcer	−1.14	1.11	−1.03	0.304	−3.31; 1.03
● Traumatic ulcer	−6.22	1.38	−4.50	0.0001	−8.93; −3.51
● Diabetic ulcer	−1.60	1.89	−0.85	0.396	−5.31; 2.10
Ulcer age	0.11	0.06	2.00	0.045	0.00; 0.23
Infection	0.92	0.42	2.18	0.029	0.09; 1.74
Constant	10.27	1.22	8.45	0.0001	7.89; 12.67

SEM=standard error of mean; 95% CI=95% confidence interval;
† Vascular ulcers were used as a comparison

Fig 6. Percentage of wounds healed at the end of each cycle
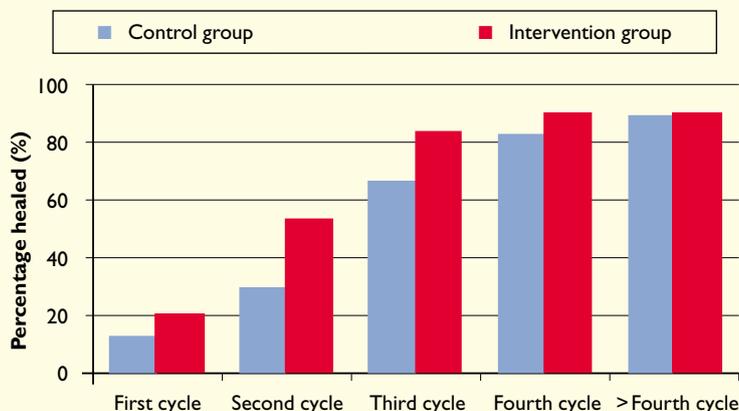
group throughout the study (paired Student's t-test, p<0.0001). In particular, the healing percentage in the ES group was statistically-significantly higher than the control group at the end of the second and third cycle of therapy. By the end of the third cycle the 83% of patients in the intervention group had achieved healing, while the control group reached a similar percentage by the end of the fourth cycle, 6 weeks later. Similar behaviour is observed for the ES group at the end of the fourth cycle. Data show that, at the end of the study, the percentage of healed patients in each group was the same (90%); however, in the ES group 2.21±0.92 cycles were necessary to achieve healing compared with 3.00±1.52 cycles in the control group (p<0.05).

Discussion

The present study was a randomised controlled clinical trial with parallel groups that investigated the efficacy of ES therapy in patients with chronic leg ulcers of the lower limb compared to standard treatment. Data collected in this study support those in the literature.[15]

The effectiveness of ES is described in the literature especially in the treatment of painful diabetic neuropathies.[16] ES treatment was shown to increase microvascular blood flow, to reduce diabetic neuropathy pain, to ameliorate the sensory tactile and vibration perception threshold and motor nerve conduction velocity compared with placebo.[11]

Only two studies suggested a role for ES in treatment of chronic painful ulcers. In 2007, Jankovic et al. published a study concerning the effect of ES on chronic painful leg ulcers of mixed aetiology (arterial, venous, mixed arterial and diabetic) in 35 patients,[12] while, in 2012, Santamato et al. published an RCT comparing the efficacy of ES to standard topical therapy in 20 patients with chronic leg ulcers.[13] This study excluded the diabetic foot ulcers, so it was possible to observe the effectiveness of ES

on nervous and vascular systems not altered by diabetes. Both the studies suggested that ES therapy accelerates wound healing and promotes an early decrease of pain associated to chronic leg ulcers.

Data collected in the present study suggest that ES treatment improves wound healing and increases control of pain compared with conventional medical therapy in patients with chronic leg ulcers of mixed aetiology, confirming preliminary data present in the literature.

The results obtained showed a significant reduction of mean VAS in the ES group compared with controls, which remained statistically significant for the entire duration of the study, from the end of the second cycle).

PUSH tool score was also seen to significantly decrease during the study for both groups; as with VAS, the mean values in the ES group were significantly lower compared with controls, from the end of the second cycle.

As these data were affected by different factors, it was necessary to perform an effectiveness analysis using complex models. This analysis assessed the difference in the trends of the variables studied (VAS and PUSH score) at different times, taking into account the possible confounding effects of covariates, such as wound aetiology, age of the lesion and the presence of infection. The complex model analysis evidenced that the ES group showed a significantly higher reduction in VAS and PUSH scores over time than the control group, even taking into account the significant influence of covariates.

In the model for VAS, the most influencing covariates were the nature of the injury and the presence of infection, while the age of ulcer was not relevant. However, for the PUSH tool model, the age of the ulcer was significant as well.

The percentage of healing in the ES group was consistently higher than the control group. Looking at the data it is possible to observe a kind of 'acceleration' in the healing process; however, by the end of the study, similar numbers of patients had healed in the two groups (90%).

In more recent studies, some of the mechanisms of action for ES in healing wounds have been identified.[17] A study conducted on patients with painful diabetic foot ulcers showed that treatment with ES induced an enhancement in cutaneous microvascular flow.[17] Moreover, it has been demonstrated that ES therapy modulates the release of angiogenetic growth factors, such as the vascular-endothelial growth factor (VEGF).[18]

This suggests that improvement in the PUSH tool score could be explained by the effect of ES on skin electric fields. It has been suggested that chronic wounds may persist because the skin surrounding the wound lacks the electrical natural stimuli required to drive the healing process.[19–21] In general,

skin is not considered an electrically-responsive tissue. Yet, it generates an electric current and experimental evidences shows that electric fields are important mediators that promote healing.[22]

Naturally-occurring electric currents in human skin wounds were measured almost 200 years ago, but only in the last decade have many of the mechanisms that regulate cutaneous electric fields been identified. It has been demonstrated that a transepithelial potential difference (TEP) in human skin drops to negative when a wound disrupts the epithelial barrier. This new potential gradient drives the electric current flow towards the more negative side, forming a laterally-orientated wound electric field.[23–25]

It has been demonstrated that this wound-generated electric field may participate in wound healing by directing cell migration.[22] The mechanisms regulating cell migration in response to an electric field are only partially identified. It has been hypothesised that the endogenous wound electric signal coupled with a different signal pathway leads to cell polarisation and migration. Many cell types, such as fibroblasts, keratinocytes and endothelial cells, exhibit this directional migratory response to electric fields, which increase during wound healing, enhancing re-epithelialisation and angiogenesis.[26–28]

The effect of ES on re-epithelialisation might be explained through the ability of the ES to restore the cutaneous physiological electrical field, increasing epithelial cell migration.

Limitations

Limitations include the lack of a real sham therapy in the comparator group receiving treatment alone, which limited our ability to assess the cause-and-effect ratio.

Conclusion

Analysis of longitudinal data analysed by simple models and complex models suggest that ES therapy had a positive, significant effect on pain reduction (VAS) and improved the ulcer healing process in terms of the PUSH tool total index compared with conventional treatment, and may have induced a significant acceleration of the wound-healing process. ∎

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