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A portable pulsed electromagnetic field (PEMF) device to enhance healing of recalcitrant venous ulcers: a double-blind, placebo-controlled clinical trial

M.J.STILLER, GRACE H.PAK, J.L.SHUPACK, S.THALER,* CLARE KENNY AND LORRIE JONDREAU

The Ronald O.Perelman Department of Dermatology, New York University Medical Center, Dermatopharmacology Section and Leg Ulcer Clinic, 550 First Avenue, New York, NY 10016, U.S.A.
**Geomed, Inc., 603 Chestnut St, Garden City, NY 11530, U.S.A.*

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Summary A prospective, randomized, double-blind, placebo-controlled multicentre study assessed the clinical efficacy and safety of pulsed electromagnetic limb ulcer therapy (PELUT) in the healing of recalcitrant, predominantly venous leg ulcers. The portable device was used at home for 3 h daily during this 8-week clinical trial as an adjunct to a wound dressing. Wound surface area, ulcer depth and pain intensity were assessed at weeks 0, 4 and 8. At week 8 the active group had a 47·7% decrease in wound surface area vs. a 42·3% increase for placebo ($P<0·0002$). Investigators' global evaluations indicated that 50% of the ulcers in the active group healed or markedly improved vs. 0% in the placebo group, and 0% of the active group worsened vs. 54% of the placebo group ($P<0·001$). Significant decreases in wound depth ($P<0·04$) and pain intensity ($P<0·04$) favouring the active group were seen. Patients whose ulcers improved significantly after 8 weeks were permitted to continue double-blind therapy for an additional 4 weeks. Eleven active and one placebo patient continued therapy until week 12, with the active treatment group continuing to show improvement. There were no reports of adverse events attributable to this device. We conclude that the PELUT device is a safe and effective adjunct to non-surgical therapy for recalcitrant venous leg ulcers.

In the U.S.A. it is estimated that leg ulcers, 90% of which are due to venous stasis, affect 0·6% of men and 2·1% of women between 60 and 69 years of age.[1] The prevalence of leg ulcers increases to 5% by the age of 90.[2] An epidemiological study in the U.K. involving nearly 1500 patients with chronic leg ulcers estimated an incidence of 1·48/1000 population.[3] The duration of ulcers reported in such studies ranges from a few months to decades with a mean duration usually greater than 10 years.[1]

The paucity of alternative non-surgical therapies for ulcers that do not respond to conventional treatment provided the impetus for this study. Our interest in the application of low-frequency, low-energy pulsed electromagnetic fields (PEMFs) to promote wound healing stems from the following: (i) successful use of PEMFs in healing more than 100,000 non-union fractures,[4,5,6] (ii) anecdotal reports of acclerated closure of chronic skin wounds overlying fractures being treated with PEMFs,[7,8] (iii) growing acceptance of experimental data demonstrating the biological effects of low-energy electromagnetic fields,[4,9,10] and (iv) historical perspective on electrical stimulation of skin to enhance wound healing.

The use of electricity as a therapy for surface wounds can be traced back more than 300 years to the use of charged gold leaf to prevent smallpox scars.[11] Interest in electrical therapy was renewed in the mid-twentieth century with the discovery of electrical properties of living systems and the use of direct current (DC) stimulation to alter surface wound healing.[12] In 1983, Foulds and Barker demonstrated the presence of a 'battery' in human skin, i.e. an electrical potential difference across the epidermis, which becomes accentuated at the periphery of the wound following injury. This increased potential difference is thought to play a role in wound repair.[13] Human clinical trials and animal experiments have shown that electrical stimulation of skin accelerates wound healing, presumably by

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augmenting the endogenous current induced by injury.[12,14,15,16] However, DC stimulation used in these studies has the disadvantage of requiring electrode placement directly in or near the wound.

PEMFs have an inherent advantage over DC systems in that the electromagnetic signal penetrates the dressing and the tissue involved. In short, pulsed magnetic fields interact with electrically conductive elements in tissue, resulting in induced currents. The basic mechanisms underlying the clinical effects of PEMFs are not clear. However, it has been suggested that PEMFs, by altering or augmenting pre-existing endogenous electrical fields, may trigger specific, measurable cellular responses such as DNA synthesis, transcription and protein synthesis.[9] Such cellular responses appear to occur within a 'window' of PEMF parameters (frequency, amplitude, timing and length of exposure).[4]

It has been reported that PEMF stimulation decreases the doubling time of fibroblasts and endothelial cells and induces differentiation of skin fibroblasts in culture.[17–19] Increased collagen synthesis, angiogenesis, and bacteriostasis are some mechanisms by which PEMFs may contribute to wound healing.[17,18] *In vivo*, electrical stimulation has been shown to increase tensile strength of surgical wounds.[20] There are also reported effects of electromagnetic fields on hormonal regulation, membrane transport, enzymatic activity, and receptor expression.[21,22]

To date, one double-blind, placebo-controlled study in the orthopaedic literature has shown that PEMF stimulation enhances the healing of cutaneous ulcers.[23] Our clinical trial differs from the former study by the innovative features of the PEMF device including its light weight and portability, qualitative and quantitative parameters of the electromagnetic stimulus, as well as stringent protocol design. We report the results of a double-blind, placebo-controlled clinical trial to assess the efficacy and safety of pulsed electromagnetic limb ulcer therapy (PELUT) as an adjunct to non-surgical management of recalcitrant venous leg ulcers.

Methods

Study design

This study was designed as a prospective, multicentre, double-blind randomized trial, to evaluate the efficacy and safety of the PELUT device as an adjunctive treatment for recalcitrant venous stasis ulcers. The following eight centres participated: UMDNJ–Robert Wood Johnson Medical School, Department of Dermatology (New Brunswick, NJ), Vascular Skin Ulcer Institute (Chicago, IL), Lebanon Vascular Surgical Associates (Lebanon, PA), Pennsylvania College of Podiatric Medicine, Department of Medicine (Philadelphia, PA), VA Medical Center, Department of Podiatry (Lebanon, PA), Albert Einstein College of Medicine, Department of Vascular Surgery (Bronx, NY), NYU Medical Center, Department of Dermatology (New York, NY). Protocol-eligible patients were randomized according to a computer-generated code based on their order of admittance to the study. Each patient was assigned either an active or an indistinguishable placebo device according to the code devised by the study sponsor, Geomed, Inc.

Study population

Thirty-one patients, each with one study ulcer, were enrolled. Eighteen patients were randomized to the active treatment group and 13 patients to the placebo group. There were no statistically significant demographic differences between the placebo and active groups, as shown in Table 1.

A protocol-eligible wound consisted of a predominantly venous, full-thickness leg ulcer with maximum linear dimension (diameter) no greater than 7·0 cm, that had demonstrated unsatisfactory healing in response to non-surgical treatment for at least 4 weeks prior to enrollment in the study. The protocol also required ulcer stability, which was defined as 15% or less change in diameter and no more than 15% change in percentage of healthy granulation tissue during the 2-week period prior to the start of PELUT therapy.

Diagnosis of venous stasis ulcers was made within 1 month prior to the week 0 visit. Pertinent physical findings included oedema and varicosities and secondary signs of venous insufficiency such as stasis dermatitis, dependent rubor, hyperpigmentation and lipodermatosclerosis. Arterial disease was excluded by the presence

Table 1. Demographic data

	Active ($n=18$)	Placebo ($n=13$)
Mean age (years)	63·3	63·8
Age range (years)	41–87	39–76
Number of men	9	8
Number of women	9	5
Mean ulcer duration* (weeks)	38·9 ± 5·2	46·8 ± 11·3
Mean ulcer area (cm^2)	7·25 ± 1·02	7·66 ± 1·62

*Each subject had one designated study ulcer.

of strong pedal pulses and adequate capillary refill.[24] In addition, patients with a history of claudication, ischaemic heart disease, or cerebrovascular disease were excluded from the study. When necessary, Doppler ultrasound, photoplethysmography, impedance plethysmography, light reflection rheography, or arteriography were obtained to establish the diagnosis of venous insufficiency and to rule out arterial disease. Decubitus ulcers or ulcers primarily due to diabetes, vasculitis, neuropathy, infection or acute ischaemia were excluded from the study. Exclusion criteria also included patients with current active deep-vein thrombosis or thrombophlebitis, patients with pacemakers and patients suffering from alcoholism, nutritional deficiency, anaemia, congestive heart failure, hepatic or renal failure, uncontrolled diabetes, malignancy, or immunosuppression.

Protocol

At week 0 patients were instructed to apply the PELUT device over the wound dressing covering their ulcer for 3 h every day. This was done for 8 weeks or until the ulcer healed, if prior to 8 weeks. Patients were allowed to continue therapy to 12 weeks at the discretion of the investigator if the ulcer showed a favourable response at 8 weeks. This decision was made without breaking the patient's device assignment code. To monitor compliance, patients kept a diary listing start and stop time of each treatment application, which was reviewed by the investigator at the follow-up visits. The total hours of PELUT use was also calculated from the visual chronometer display on each device. To ensure proper functioning of the PELUT devices, each was inspected by the manufacturer prior to initiation of therapy and at the conclusion of treatment.

In addition to daily treatment with the PELUT device, all patients received ancillary topical treatment. The PELUT system was designed as an adjunctive therapy, so the topical treatment at each of the study centres was chosen by the investigator at each centre. Wound dressings used are summarized in Table 2. All regimens included an elastic compression wrap at all times (3-inch Ace Bandage®), which exerted approximately 20 mmHg pressure at ankle level. Leg elevation for a minimum of 3 h daily was also included in all ancillary treatment regimens. Patients who were unable to adhere to the requirement for leg elevation or whose occupation and/or life-style required prolonged standing were excluded from the protocol. The patients were seen in clinic at 2-week intervals to monitor safety and compliance. Efficacy parameters were assessed at weeks 0, 4, 8 (and 12), at which time photographs of the study ulcers were taken. The protocol was approved by the Institutional Review Boards of all participating institutions prior to initiation.

Table 2. Ancillary treatment

Treatment*	Active ($n=18$)	Placebo ($n=13$)
Duoderm®†	0	1
Gentamicin ointment + Duoderm®†	3	2
Mupirocin ointment + Vigilon®	2	1
Mupirocin ointment + non-adherent gauze	8	6
Elase® ointment + gauze	3	2
Unna's boot‡	2	1

* All regimens included an elastic compression wrap (Ace Bandage®) and leg elevation in addition to topical therapy.

† Duoderm® hydroactive dressing is an occlusive, oxygen-impermeable sheet of hydrophilic particles encased in an inert hydrophobic polymer matrix placed on an adhesive plastic backing.[25]

‡ Unna's boot is a moist paste bandage impregnated with zinc oxide, calamine lotion and glycerin, wrapped snugly around the leg in direct contact with the ulcer, worn continuously and changed weekly. It provides topical wound therapy as well as compression. The boot produces a pressure gradient between ankle and calf, as do support stockings, yielding similar therapeutic efficacy in venous stasis ulcers.[26]

PELUT device

The PELUT system consisted of a control unit, containing a signal generator and a rechargeable 9-V battery, attached by an expandable cable to the electromagnetic transducer which was strapped over the wound dressing with an elasticized Velcro strap. The control unit and the transducer combined weighed 550 g (Figs 1 and 2). The transducer was an air coil employing magnetic focusing elements to provide improved efficiency (about 35%) and one-sided output. The PELUT system, which is designed and manufactured by Geomed Inc. delivers a low-energy PEMF that induces a low level, non-thermal electrical field of approximately 0·06 mV/cm. The signal is a 3-part pulse (+, −, +) of 3·5 ms total width and a duty cycle of 25%. The amplitude is bidirectional with delta B of approximately 22 Gauss. This bidirectional, quasi-symmetrical magnetic stimulus, in contrast to more frequently used unidirectional signals, minimizes energy consumption and patient exposure to peak magnetic fields. Parameters of the PELUT stimulus are derived from the PEMFs which have been used effectively to treat non-union fractures. Approximately 50% of these frac-

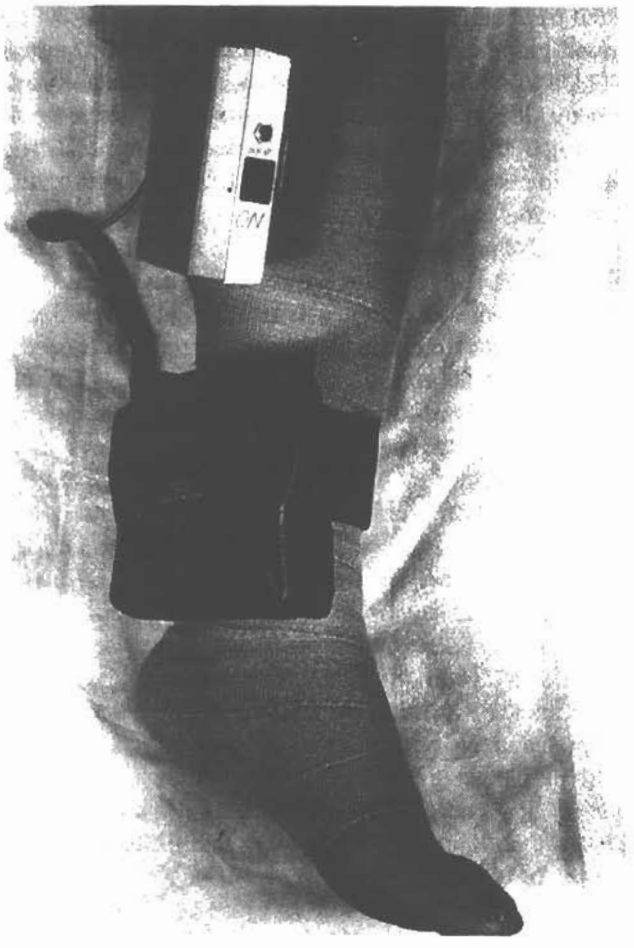

Figure 1. Pulsed electromagnetic limb ulcer therapy (PELUT) device. The electromagnetic transducer is placed over the wound dressing with an elasticized Velcro strap. The transducer is attached by an expandable cable to the control unit (signal generator and a rechargeable battery) which can be worn over a belt.

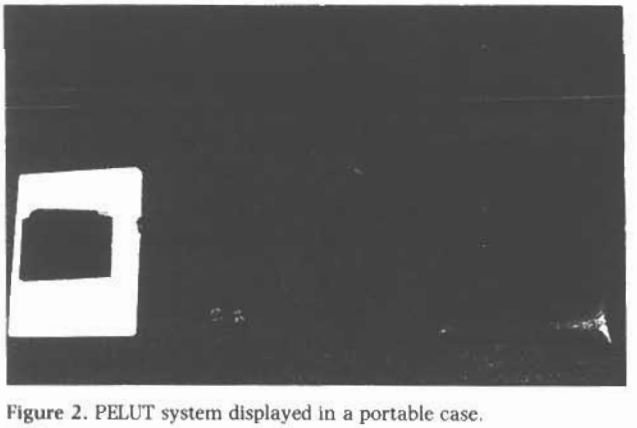

Figure 2. PELUT system displayed in a portable case.

tures involve the tibia, so the available safety data from more than 100,000 orthopaedic patients could be extrapolated to our use of comparable PEMF signals to treat leg ulcers. In addition, earlier *in vitro* studies employing the PEMF parameters described in this study have demonstrated measurable biological effects (N. Guzelsu *et al.*, unpublished data). All PELUT devices operated silently with no perceivable thermal, tactile or vibratory sensation. Neither patients nor investigators were able to discern any difference between active and placebo devices.

Efficacy parameters assessed at weeks 0, 4, 8 (and 12)

Wound surface area. The inner edge of the ulcer (border of epithelium) was traced on a Mylar sheet, and the surface area was calculated using computer image analysis by KGL, Inc. (Broomall, PA, U.S.A.). When this technique was attempted by multiple blinded investigators prior to initiation of the study, the degree of variation in wound area was less than 5%. This variation was primarily due to the thickness of the marker tip and to a lesser extent the difficulty in visualizing the ulcer border. Equipment used included: Magiscan 2B Image Analyzer (Joyce Loebl, Gateshead, U.K.), Dage Series 61 video camera (Dage-MTI, Inc., Michigan City, IN, U.S.A.), and software menu program developed by Joyce Loebl.

Wound depth. Wound depth, a secondary efficacy parameter, was measured at the deepest point using Digimatic Calipers (manufactured by Mitutoyo Corporation, Paramus, NJ, U.S.A.) or equivalent Digi-Met Electronic Calipers (Flexbar-Preisser Machine Corporation, Central Islip, NY, U.S.A.). Depth measurements obtained by these devices were significantly more accurate and reproducible than those obtained with a straight ruler as employed in earlier American studies.[27]

Granulation tissue. The quality and the quantity of the granulation tissue were clinically assessed by the investigator as the percentage of wound area with healthy bright pink or red-coloured tissue, or unhealthy grey or light pink-coloured tissue and necrotic tissue.

Clinical global assessment. The investigators' clinical global assessment of healing status was based on the eight-point scale outlined below: +4, healed; +3, marked improvement; +2, moderate improvement; +1, slight improvement; 0, no worse; −1, slightly worse; −2, moderately worse; −3, markedly worse. The primary factor in the clinical global assessment was

wound area. Ulcer depth, appearance of granulation tissue and pain were also considered. Other factors including changes in oedema, stasis dermatitis and post-inflammatory hyperpigmentation were given lesser consideration.

Pain intensity. Patients reported pain intensity at the wound site on a four-point scale: 0, none; 1, mild; 2, moderate; 3, severe.

Statistical analysis

All analyses were performed with the Statistical Analysis System (SAS Institute Inc., Cary, NC, U.S.A.) on an IBM 3081 mainframe computer. The active vs. placebo differences were analysed for statistical significance by computing one-sided P values from analysis of variance (ANOVA) and from Kruskal–Wallis analysis of variance by ranks (rank-ANOVA).[28,29] The rank-ANOVA was included because it does not require the statistical assumptions of a Gaussian distribution or homogeneity of variances.

Results

Treatment with the active PELUT device resulted in statistically significant improvement in all efficacy parameters compared to treatment with the placebo device. At week 0 (baseline), there was no statistically significant difference between the two treatment groups with respect to any of the efficacy parameters. However, it is noteworthy that the ulcers in the placebo group were rated more painful at baseline, and the difference in this secondary efficacy parameter was marginally significant. Four patients (one active, three placebo) failed to complete the study, defaulting between days 28 and 38. One patient was lost to follow-up and could not be contacted by telephone or certified mail. The other defaulters cited personal reasons not related to adverse events or lack of progress during study participation.

Wound area

The week 0 and week 8 wound surface areas for the active and placebo groups are shown in Figure 3. The changes in wound surface area were a 47·1% decrease for active and 48·7% increase for placebo ($P<0·0002$). For the patients who discontinued the study prior to day 42, week 8 wound area was determined by two methods: (i) estimation by linear extrapolation to day 56, or (ii) use of the last observed wound area in place of week 8 value.

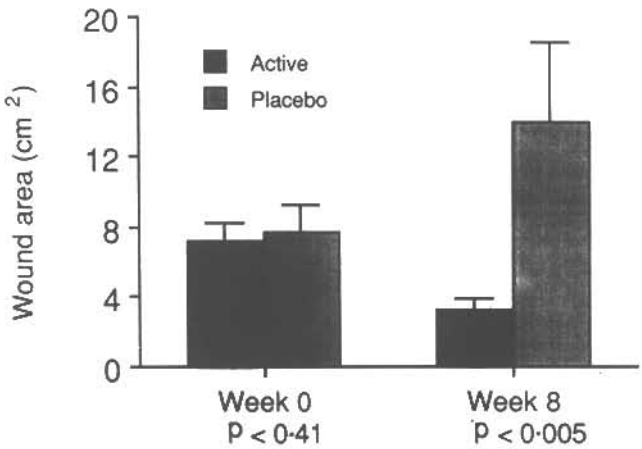

Figure 3. Wound surface area at baseline and after 8 weeks of treatment with PELUT or placebo device.

The results based on the last observed values were similar to those based on extrapolated week 8 values: the active group averaged a 47·7% decrease in wound surface area vs. a 42·3% increase in wound area for the placebo group ($P<0·0002$). Change and per cent change in wound area were calculated for each patient in order to account for variability in wound size. In both active and placebo groups, there was no correlation between either the initial ulcer size or the type of ancillary treatment and the degree of subsequent change in wound area.

Wound depth

In the active group the average wound depth decreased from $0·24 \pm 0·04$ cm to $0·13 \pm 0·02$ cm. In the placebo group the average wound depth was $0·26 \pm 0·01$ cm at baseline and $0·25 \pm 0·03$ cm after treatment ($P<0·04$) (Fig. 4).

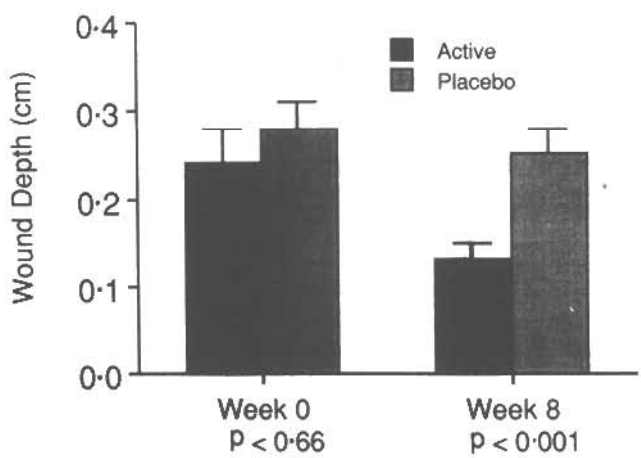

Figure 4. Wound depth at baseline and week 8.

Granulation tissue

In the active group the average percentage of healthy granulation tissue increased from 68·1±6·4% to 83·2±4·4%. In the placebo group the average percentage of healthy granulation tissue was 67·1±8·3% at week 0 and 67·5±7·7% at week 8 ($P<0·04$). There was a 14·1% decrease in unhealthy granulation tissue for the active group and 0% change for the placebo group ($P<0·04$).

Investigators' clinical global assessment at week 8

Fifty per cent of the active group healed or markedly improved compared with 0% of the placebo group. In contrast, 54% of the placebo group was rated worse compared with 0% of the active group ($P<0·001$).

Pain intensity

Wound site pain showed a score decrease of 0·61 (on the four-point scale mentioned previously) in the active group and a score decrease of 0·15 in the placebo group ($P<0·04$).

Twelve-week treatment group

Of the 12 patients who continued double-blind PELUT therapy to week 12, 11 patients were from the active group and only one patient was from the placebo group. At week 12, the active patients exhibited 66·3% decrease in wound surface area, representing further improvement from their 47·9% decrease in wound area at week 8. The placebo patient, who at week 8 had a 39·2% decrease in wound area, exhibited only a slight further decrease in wound area to 42·8% at week 12.

Adverse effects

There were no reports of patient complaints or adverse events attributable to the use of the PELUT device.

Discussion

The results of this study indicate that PEMF stimulation effectively and safely enhances the healing of recalcitrant venous stasis ulcers. Active PELUT therapy, 3 h daily for 8 weeks, led to a 47% decrease in wound area, a significant decrease in wound depth, 15% increase in healthy granulation tissue, and improved pain intensity scores. The patients who continued active treatment to 12 weeks exhibited further improvement (66% decrease in wound area). It is also noteworthy that half of the PEMF-stimulated ulcers healed or improved markedly, compared with none in the placebo group.

It is well known that venous leg ulcers may spontaneously improve or worsen. Ieran *et al.*, evaluating the effect of a unidirectional PEMF device on venous ulcers reported significant spontaneous healing in their control group (30% decrease in wound size over 90 days).[23] However, the control group in our study exhibited a 48% increase in wound area. It is possible that the ulcers in this study, because of stringent protocol inclusion–exclusion criteria and because the study sites were tertiary referral centres, were particularly recalcitrant. The relatively small number of patients enrolled in this clinical trial may have also contributed to the placebo effect, but our rigorous statistical analyses preclude this as a major factor. A recalcitrant ulcer in this study was defined as a stage II or III ulcer that had demonstrated poor healing in response to topical treatment for at least 4 weeks prior to enrollment in the study. In addition, wound size limitations and wound stability (<15% change in wound diameter and granulation tissue during 2 weeks prior to week 0) provided a homogeneous group of recalcitrant ulcers in this clinical trial. In the Ieran study, recalcitrance and wound stability were not protocol requirements. Although we cannot rule out a possible adverse effect of wearing the placebo device, this is unlikely given the light weight and portability of the device, as well as the improvement and absence of adverse events in the active group.

Whether PEMF stimulation facilitates ulcer healing by simply accelerating the normal healing process or by altering the mechanism of wound healing cannot be ascertained from this investigation. In a recent review of clinical applications of electric fields in soft tissue repair, Canaday and Lee concluded that electric or magnetic fields may accelerate wound healing only under circumstances in which the healing process is delayed or arrested, i.e. conditions of deficient or absent electrical current.[30] It is also of interest that to date, no healing enhancing agent has significantly altered the kinetics of normal healing.[30]

In vitro studies have demonstrated diverse cellular responses to PEMFs that may be relevant to wound healing. For example, migration of cultured fibroblasts and epithelial cells in perpendicular alignment to applied electrical fields is a well established phenomenon.[10,21,31] Stimulation with sinusoidal electromagnetic fields has been shown to induce differentiation of human skin

fibroblasts and increase collagen and total protein synthesis.[19] PEMF stimulation employing physical parameters similar to those used in the present investigation resulted in enhanced proliferation of fibroblasts, as measured by increased DNA synthesis (N.Guzelsu *et al.*, unpublished data). Increased angiogenesis in response to PEMFs is also thought to play a role in wound healing. Yen-Patton *et al.* reported that endothelial cells in culture grow at a higher rate and reorganize into three-dimensional vessel-like structures in the presence of a PEMF.[18] The specificity of the electromagnetic stimulus–response relationship is clearly demonstrated in the transcription studies by Goodman *et al.*[9] Exposure of human cultured cells (HL 60) to PEMFs with different characteristics resulted in signal-specific quantitative changes in RNA transcripts.[32] Despite the growing literature of the basic mechanisms underlying PEMF's biological effects, it is difficult to extrapolate such data to account for *in vivo* events. A systematic approach should be taken to characterize the 'windows' of PEMF parameters for cellular responses, as well as for complex *in vivo* events such as wound healing.

In light of recent controversy regarding the potential health hazards of environmental electromagnetic fields, the safety of PEMFs is addressed here. First of all, PEMFs were designed to induce electrical fields in tissue similar to those which normally result from electrokinetic events when tissues are mechanically deformed.[4,22] Second, more than 100,000 cases of non-union fractures and aseptic necrosis have been treated with PEMFs without any reported adverse effect.[6] Third, biological effects of PEMFs have been shown to arise within specific windows of stimulus parameters; therefore, we cannot extrapolate the effects of specified conditions to all PEMFs. Furthermore, the electrical field induced by a PEMF device is localized and its intensity decreases rapidly with increasing distance from the source. In addition, the energy carried by such low frequency PEMFs is thought to be too weak to break chemical bonds or have thermal effects.[9] Epidemiological data correlating environmental electromagnetic fields (power lines, electric blankets, video data terminals, etc.) with cancer, fertility and developmental problems have thus far been inconclusive.[22,33,34]

We conclude from this study that PELUT is an effective and safe adjunct to non-surgical management of recalcitrant venous leg ulcers. Additional studies are being initiated to confirm these results in a larger population and to evaluate the applicability of the PELUT system in the management of recalcitrant ulcers due to causes other than venous stasis.

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