The Use of Low Energy Photon Therapy (LEPT) in Venous Leg Ulcers: A Double-Blind, Placebo-Controlled Study

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BACKGROUND. *Venous ulcers are estimated to be present in 0.2 to 0.4% of the population. Although new therapies have significant promise, nonhealing ulcers still represent a significant problem.*
OBJECTIVE. *To evaluate the efficacy of low energy photon therapy (LEPT) in the treatment of venous leg ulcers.*
METHODS. *A placebo-controlled, double-blind study using low energy photon therapy was performed in nine patients with 12 venous ulcers. Treatment was given three times a week for 10 weeks, using two monochromatic optical sources. One source provided a wavelength (λ) of 660 nm (red) while the second source delivered a wavelength of 880 nm (infrared). Two optical probes were used, one consisted of an array of 22 monochromatic sources, operating at a wavelength of 660 nm and covering an area 6 × 10 cm². The second probe had seven infrared sources, operating at a wavelength of 880 nm and covering an area of 4 cm². The above configuration of optical probes was selected to cover the majority of the ulcer area being treated. The patients who were randomized to placebo treatment received sham therapy from an identical-appearing light source from the same delivery system.*
RESULTS. *Nine patients with 12 venous ulcers were randomized to receive LEPT or placebo therapy. At the conclusion of the study, the percentage of the initial ulcer area remaining unhealed in the LEPT and placebo groups was 24.4% and 84.7%, respectively (P = 0.0008). The decrease in ulcer area (compared to baseline) observed in the LEPT and placebo groups was 193.0 mm² and 14.7 mm², respectively (P = 0.0002). One patient dropped out of the study, complaining of lack of treatment efficacy; he was found to be randomized to the placebo group. There were no adverse effects.*
CONCLUSION. *In this placebo-controlled, double-blind study LEPT was an effective modality for the treatment of venous leg ulcers.* © *1998 by the American Society for Dermatologic Surgery, Inc. Dermatol Surg 1998;24:1383–1386.*

Venous stasis ulcers are the most common form of leg ulcers.[1] In population-based epidemiologic studies the point prevalence of venous ulcers has ranged from 0.2 to 0.4%.[2] Leg and foot ulcers become more common with age. In fact, the prevalence of venous leg ulcers in individuals about 70 years is estimated to be 1% to 4%.[3,4] Management of leg ulcers includes support and compression bandages, dressings, treatment of coexisting infection and limb elevation.[5–12] In some cases oral medications and surgery may be of benefit.[13,14] Other treatment modalities include ultrasound,[15,16] low energy laser/photon stimulation.[17–35] Different optical sources of low energy photons, both coherent (lasers, laser diodes) and noncoherent (light emitting diodes) have been used to treat ulcers. In this double-blind, placebo-controlled study to treat venous leg ulcers, the low-energy photon system provided a three-dimensional photon distribution in the ulcer area and operated at irradiation intensities that were so low that the biological effects were thought to occur as a direct result of the irradiation rather than by a heating effect (ie, non-thermal events).[26,28,35]

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Methods

Patients

Nine patients (five men, four women; mean age, 62.4 years; range, 37–76 years) with 12 venous leg ulcers were entered into this 10 week double-blind, placebo-controlled outpatient study. The patients demonstrated stasis changes and had clinically normal arterial foot pulses. Subjects were randomized to receive LEPT or placebo using the same device. The treatments were administered by the same operator in a double-blind manner, so that neither the clinician performing the measurement of the ulcer size, nor the technician providing the LEPT/placebo therapy, or the patient were aware if they were receiving active or placebo therapy. Placebo therapy consisted of light of the same color given using the same delivery system. The randomization was performed by blinded support staff. The ulcers were treated three times a week for a period of 10 weeks, that is, a total of 30 treatments.

Exclusion Criteria

Patients with malignancy, or with immunocompromised status, or with ulcers ≥12 cm² area. All subjects provided in-

formed consent after the nature of the study and treatment had been explained to them.

Low-Energy Photon Source Specifications

These have been described elsewhere.[35] Low energy photons with wavelengths in the visible and near infrared wavelength range (400–1,000 nm) and unlike ultraviolet or x-ray irradiation do not possess sufficient energy to produce biomolecular ionization. Treatments were administered using a low energy photon therapy device with microprocessor-controlled, multiple monochromatic optical source probes (International Medical Instruments Inc., Ontario, Canada). One probe with 22 monochromatic red sources (R-22 probe) operated at a wavelength of 660 nm, in a continuous wave mode with a beam power 6 mW per head, energy density at 4 J/cm^2 per head and covering an area 6 × 10 cm^2. The second type of probe had seven monochromic infrared (invisible) sources (IR-7 probe) operating at a wavelength of 880 nm with a beam power 12 mW per head, energy density 4 J/cm^2 per head, pulse frequency 4 Hz and covering an area 4 cm^2. The output power was checked every 2 weeks. The parameters outlined above were optimized following extensive preliminary research on cutaneous ulcers.

Low-Energy Photon Therapy of Ulcers

The healthy-appearing skin at the periphery of the ulcer was treated with the IR-7 probe for 30 seconds. Then the ulcer was treated using the R-22 probe for 180 seconds. The probes were held perpendicular to the skin surface close to, but not in contact with, the ulcer. A typical treatment session lasted a total of 5 to 6 minutes.

Ulcer Care

For the duration of the study leg ulcers were cleaned with saline followed by a dry dressing. Patients were allowed to apply a moisturizer to the periphery of the ulcer; no other therapies that may enhance healing of the ulcer were permitted without prior discussion with the physician.

Evaluation of Response

Before commencing LEPT, and at weekly intervals, the size of the ulcer was measured and photographs were obtained at baseline and at weeks 3, 7 and 10 following the start of treatment. The area of the ulcer was calculated by an individual who was not aware of the nature of treatment, LEPT or placebo being provided to the patient.

Statistics

If multiple ulcers were present in a patient, then the total ulcer area was used in the analysis. Patients were randomly assigned to the LEPT or placebo group. The rate of healing was calculated from the area of the ulcer (mm^2) divided by the duration of treatment. Individual plots were made for each patient to display the rate of healing throughout the treatment duration. Comparative t-tests were used to evaluate the randomization of subjects to the study groups based on the following parameters: age, ulcer duration, and baseline ulcer area. Analysis of variance (ANOVA) were performed at weeks 3, 7, 10 to evaluate the efficacy of LEPT as a treatment modality for venous ulcers. The least significant difference (LSD) method was used to compare the mean treatment results. Regression analysis was performed at week 10 for the group receiving LEPT in an attempt to determine an equation for the percentage of ulcer area that remained unhealed so that this could be applied to other population of venous leg ulcers.

Results

Nine patients with 12 venous ulcers entered into the study. One patient dropped out of the study after 3 weeks complaining of lack of treatment efficacy and has not been included in the efficacy analysis carried out at week 10; this patient was found to be randomized to the placebo group. Another patient, also receiving placebo therapy, developed a secondary Staphylococcal infection. This patient used topical fucidic acid as adjunctive therapy and was allowed to continue with the study. The data from this patient has been included in the statistical analysis. No other patients in either the LEPT or placebo groups used adjunctive therapy.

The descriptive statistics and comparative tests (P values) for weeks 0 (baseline), 3, 7, and 10 are summarized in Table 1. Subjects were adequately randomized using the parameters of age ($P = 0.98$) and baseline ulcer area ($P = 0.92$). When the mean ± SE for ulcer duration of LEPT (105.8 ± 36.0 weeks) and placebo (36.0 ± 21.6 weeks) groups were compared, a bias was evident in the data ($P = 0.02$). In order to determine the direction of the bias, a one-sided t-test was performed, thereby testing the null hypothesis (Ho: $t_1 - t_2 > 0$). A significant P value was obtained indicating that the null hypothesis was rejected in favour of the alternative, i.e., the randomization bias was toward the placebo group in which the ulcers were of a significantly shorter duration compared to the LEPT group. Despite this, LEPT was found to be significantly more effective than placebo in the treatment of venous ulcers.

The parameters used for comparative analysis were: change in ulcer area compared to baseline (mm^2), percentage of ulcer that remained unhealed compared to baseline, and the rate of healing (mm^2/week) (Table 1). LEPT was found to be significantly more effective than placebo at each of weeks 3, 7 and 10 when the efficacy parameters were: change in area of ulcer ($P = 0.0003$) and percentage of ulcer that remained unhealed ($P = 0.04$) (Figure 1), each compared with baseline.

Within the first 3 weeks of treatment, the average percentage of ulcer area that remained unhealed in the LEPT group drastically decreased by 54.8%. During the same time interval, the average percentage of ulcer area that remained unhealed in the placebo group increased by 24.0%, i.e. increase in size compared to baseline ($P = 0.0003$). At week 10 (end of study) the average percentage of ulcer area that remained unhealed in the placebo group was 84.7%, compared to 24.3% for the LEPT

Table 1. Response of Venous Ulcers to LEPT and Placebo

Variables (mean ± S.E.)	*Group 1 Placebo Therapy*	*Group 2 LEPT*	*P Value Between the 2 Groups*
Age of patients (yrs)	64.7 ± 9.4	61.0 ± 7.8	0.98
Duration of ulcers (wks)	36.0 ± 21.6	105.8 ± 36.0	0.02
Baseline area of ulcers (mm^2)	200.3 ± 30.2	406.4 ± 210.7	0.92
Week 3			
Change in ulcer area compared with baseline (mm^2)	−47.0 ± 12.1	126.2 ± 51.2	0.0003
Percent of ulcer area that remains unhealed	124.0 ± 6.3%	45.2 ± 13.2	0.005
Rate of healing (mm^2/wk)	−15.67 ± 2.9	42.1 ± 17.0	0.024
Week 7			
Change in ulcer area compared with baseline (mm^2)	23.3 ± 30.1	185.2 ± 67.8	0.0003
Percent of ulcer area that remains unhealed	83.4 ± 16.4%	27.0 ± 13.3%	0.04
Rate of healing (mm^2/wk)	3.33 ± 2.9	26.44 ± 9.7	0.056
Week 10			
Change in ulcer area compared with baseline (mm^2)	14.7 ± 51.2	193.0 ± 70.4	0.0002
Percent of ulcer area that remains unhealed	84.7 ± 26.5%	24.3 ± 13.8%	0.008
Rate of healing (mm^2/week)	1.46 ± 3.6	19.34 ± 7.5	0.055

group (P = 0.0002), suggesting that LEPT is significantly more effective than placebo.

When the rate of healing was compared for the LEPT and placebo groups (Table 1), within the first three weeks of therapy, the rate of healing for the LEPT group had increased to 42.1 mm^2/week, while the placebo group displayed a negative rate of healing of −15.67 mm^2/week (P = 0.024). At the conclusion of the study, the rate of healing in the LEPT and placebo groups was 19.34 ± 7.5 and 1.46 ± 3.6 mm^2/week, respectively (P = 0.055).

Regression analysis was performed for percentage of ulcer area that remained unhealed in the LEPT group (compared to baseline) using the duration of ulcer and initial ulcer area at baseline as independent variables. The equation used to predict the percentage of ulcer area that remained unhealed, compared to baseline, is:

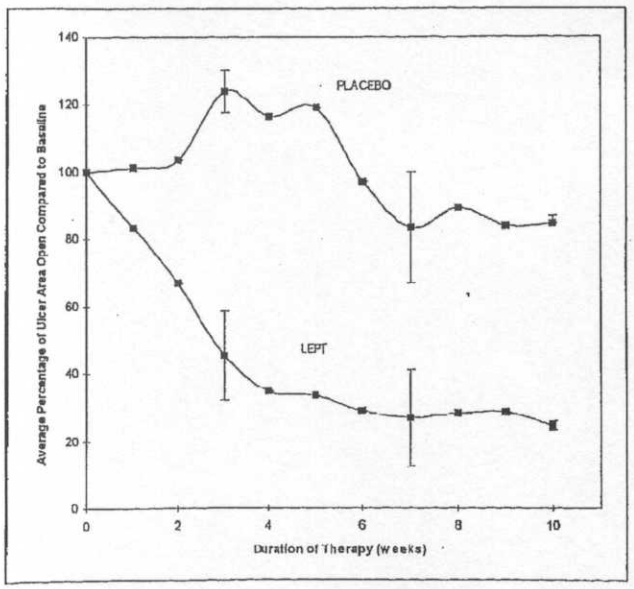
Predicted percentage of ulcer area that remains unhealed at week 10 =

− 7.8 + 0.07 *initial ulcer area*

+ 0.05 *ulcer duration.*

Further studies on a larger sample population are required to test the validity and robustness of this equation.

Figure 1. *Percentage of ulcer area that remained unhealed (mean ± SE) compared with baseline during LEPT and placebo therapy for venous leg ulcers.*



Discussion

In some animal studies low energy laser therapy may have a beneficial effect in wound healing[26,37–39]; however, this has not always been the case.[28,30,34–36,40] Similarly, LELT has been reported to be of help in some human trials,[18] but not others.[31,41] The poor response to LELT may be explained by the lack of optimization of parameters which determine the clinical response, e.g. power output and three dimensional energy density of the system, and wavelength and waveform of the optical source.[20,42] To overcome shortcomings with low energy lasers, we used other low-energy photon sources with a three-dimensional photon distribution and a set of parameters optimized for the treatment of venous leg ulcers.

In an earlier open, uncontrolled study we observed that LEPT was effective in the treatment of venous leg ulcers.[35] In the present double-blind, placebo-controlled study we have demonstrated that LEPT is significantly more effective than placebo in the treatment of venous leg ulcers. The findings need to be confirmed in a study

with a larger sample population. Also, it remains to be seen whether LEPT will eventually be used as monotherapy for venous leg ulcers or become an agent that is used in combination with other established modalities.

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