Visible Light-Induced Healing of Diabetic or Venous Foot Ulcers: A Placebo-Controlled Double-Blind Study

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Abstract

Background and objectives: Non-healing ulcers represent a significant dermatological problem. Recently, conventional therapy-resistant chronic ulcers have been treated with low energy lasers or light-emitting diodes in the visible and near IR region, but only a few placebo-controlled double-blind studies have been performed to support the efficacy of this approach. The aim of the present study was to evaluate the efficacy of a broadband (400–800 nm) visible light device in the treatment of leg or foot ulcers. Methods: A placebo-controlled double-blind study using broadband light source (400–800 nm) was performed on patients with diabetic foot ulcers or patients with chronic leg ulcers. The treatment group was illuminated with 180 mW/cm2 broadband light twice a day for 4 min/session, while patients in the placebo group received non-healing light fluency (10 mW/cm2) projections. The treatment group included 10 patients with a total of 19 ulcers, whereas in the placebo group, 6 patients had 6 ulcers. The follow-up period was 12 weeks. Results: At the end of the follow up, all the wounds were closed in 9 out of 10 patients (90%) from the treatment group, whereas in the placebo group only 2 out of 6 patients exhibited closed wounds (33%). The reduction in wound size in the treatment group versus the placebo group was 89% and 54%, respectively. Conclusions: In this small scale placebo-controlled double-blind study, broadband (400–800 nm) visible light was an effective modality for the treatment of leg or foot ulcers.

Introduction

Low energy light treatments (LEL) in the red and near IR region are a novel treatment for non-healing human wounds. However, very few good clinical studies and well-controlled investigations can be found in the literature.1,2 Nevertheless, significant literature demonstrates the stimulatory effects of light on cell cultures. For low-energy visible light to have any effect on a living biological system, the photons must be absorbed by electronic absorption bands belonging to some molecular chromophore or photosensitizer.1 The basic premise of LEL is that the light stimulates cell activation processes, which in turn intensify physiologic activity. Healing is essentially a cellular process, and light energy initiates a cascade of reactions.2 Visible and near IR light can be absorbed by cellular photosensitizers such as cytochromes, flavins/riboflavins and nicotinamide adenine dinucleotide phosphate (NADP).3 Absorption of light by these photosensitizers causes their excitation and relaxation by transferring electrons to O2*, thereby generating reactive oxygen species (ROS).4 ROS are probably best known in biology for their ability to cause oxidative stress. They can damage DNA, cell membranes, and cellular proteins and may lead to cell death.5 This phenomenon is exploited in photodynamic therapy (PDT). However, low ROS fluxes play an important role in the activation and control of many cellular processes, such as the release of transcription factors, gene expression, muscle contraction and cell growth.6,9 In a previous study,9 we showed that oxyradicals are created mainly by the flavins at the 400–500 nm range of the visible light. Various devices have been implemented in phototherapy, especially to induce wound healing. The most prevalent to date are low level lasers (~10 mW/cm2) and LEDs, in the red and near IR range, which typically produce low energy intensities (10–50 mW/cm2) at a band width of ~10 nm. However, because the absorption bands of cytochrome oxidase and flavoproteins are quite wide,10 and because the specific characteristics of laser light, such as coherency and polarization, have not been proven to be relevant for the light–tissue interaction and are lost through scattering in tissue,11 we experimented with a broadband visible light (400–800 nm) for photobiostimulative purposes. We found that at the
appropriate energy dose, similarly to LEL, broadband visible light produces ROS, and increases intracellular Ca$^{2+}$ concentration. Also, fibroblast proliferation is enhanced following broadband visible light irradiation.

In a previous preliminary observational study conducted on 20 patients with diabetic and venous ulcers, irradiation with broadband (400–800 nm) visible light resulted in a complete cure of 70% of the patients. This encouraged us to perform the present double-blind controlled study in which the treatment group was illuminated with 180 mW/cm$^2$ broadband (400–800 nm) visible light, and the placebo group was illuminated with the same device, but set to deliver light of negligible intensity.

Methods

Patients and study design

Both female and male patients with unsuccessfully treated diabetic or venous foot ulcers, grade 1 or 2 (venous ulcer $<4\text{ cm}^2$) of at least 8 weeks’ duration, were recruited to a double-blind placebo-controlled randomized study. The study took place at the Kaplan Medical Center, Rehovot, Israel. The study protocol was approved by an ethics committee and the Ministry of Health (approval number HT 2278) and was performed according to the Helsinki Committee approval, ICH GCP guidelines, and ISO 14155.

Inclusion criteria were:

- Having a diabetic foot ulcer or a venous leg ulcer of at least 8 weeks’ duration.
- Having ulcers that had not improved after prior conventional medical treatments, which included debridement, antibiotics, various ointments, and the use of elastic socks in cases of vascular dysfunction.
- Having diabetic foot ulcers, if the ulcer was of grade 1 or 2 according to Wagner’s classification. These would be superficial ulcers with no subcutaneous involvement (grade 1), or deeper sores reaching the subcutaneous tissue level in which the ulcer extension involves ligament, tendon, joint capsule or fascia (grade 2).
- Having a venous leg ulcer $<4\text{ cm}^2$.

Patients with any of the following conditions were excluded from the study:

- Severe infection.
- Having received antibiotic treatment during the week prior to the study.
- Severe vascular illness, characterized by an ankle brachial index of $<0.5$, being a candidate for vascular surgery, or having undergone revascularization surgery within 10 weeks prior to the study.
- Photosensitive diseases.
- Malignancies or renal dysfunction.
- Being on immunosuppressive medications or having a creatinine level of $>2\text{ mg\%}$.
- Pregnancy.
- Being on dialysis.
- Anemia (Hb of $<9\text{ gr\%}$).
- A serum albumin level of $<3\text{ mg\%}$.

In addition:

- All diabetic patients were measured for diabetic neuropathy, by a monofilament screening.

All patients signed an informed consent prior to inclusion in the study.

Treatment

Following review of the patient’s medical history and a physical examination, all diabetic patients had a radiograph of their foot and a vascular evaluation by Doppler. Patients’ ulcers were cleaned, debridement was performed if needed, and local care, including daily application of a pad of gauze soaked with saline, was performed. Wound dressing was used in both the control and the treatment group.

Together with the usual wound care, patients were randomized to treatment with either the phototherapy device set to therapeutic levels of the Vireo (QRay Ltd., Haifa Bay, Israel), or the phototherapy device set to an ineffective low intensity (placebo). The randomization of patients to treatment with the therapeutic or non-therapeutic device was performed by a person who was not involved in the evaluation of the study. A simple random allocation generated a number for each device. The devices were similar in all aspects; except for the number on the device itself, which encoded its light intensity. The patients and the investigators were blind to the number allocation, as both the placebo and the treatment devices were identical in design and both emitted light. Patients were instructed to treat their wound twice a day by using the Vireo (Fig. 1) over the entire wound area at a distance of 2 cm, each time for 4 min/treatment. Patients, who exhibited several distant wounds, were instructed to treat each wound for the full treatment time. Each patient kept a diary in which the treatments were logged. Following the light/placebo treatment, the wounds were dressed with a saline solution and sterile gauze. Patients with venous ulcers were instructed to bandage the ulcer with elastic bandage or stocking.

In addition:

- The use of Regranex was forbidden during the month prior to the study, to negate possible late effects of this ointment.

FIG. 1. The Vireo while in use in ordinary clinic treatment.
Patients visited the diabetic foot clinic at the Kaplan Medical Center once a week for wound care. During each visit, wounds were measured and photographed, and the patient was monitored for any adverse events, including possible skin burn or irritation. In addition to following Wagner's classification for foot ulcers, the wounds were measured according to a semiquantitative method suggested by the FDA, in which the maximal width/length is measured. Both home treatment and follow up visits continued for 12 weeks. In addition, 1 month after recovery each patient was invited to the clinic to confirm lack of recurrence of the ulcer.

Phototherapy device

A prototype of the Vireo device was used in the present study. The Vireo is a CE marked broadband light device (400–800 nm) (Fig. 1). Figure 2 represents the spectrum of the device. The devices used in the study were disabled of their capacity to allow the physician to control the treatment parameters. It should be noted, however, that the Vireo device for ordinary clinic use does allow physicians to control treatment parameters according to their assessment of the wound (light intensity and other parameters). This feature of the Vireo, of applying different light energy levels, is implemented by its desktop unit (Fig. 1). The device is then provided for home use by the patient.

In our study, the treatment group was illuminated with 180 mW/cm² broadband light, whereas patients in the placebo group received non-therapeutic light intensity (10 mW/cm²) irradiations. In our first, observational study we used broadband (400–800 nm) visible light, at 40 mW/cm². Realizing that the blue part of the visible range is mostly important for nitric oxide (NO) formation, we decided to increase the intensity of our device in order to overcome its low penetration into the tissue. The present protocol, using 180 mW/cm² twice a day, was assessed after some small clinical studies using light devices at higher fluences, showed good wound closure results.

Results

Twenty patients were recruited to the study from August 2006 until June 2009. The low recruitment rate was a result of the restrictive study design, i.e., a placebo-controlled study limited to non-healed ulcers. Four patients were excluded from analysis; 3 patients (2 from the placebo and 1 from the treatment group) were excluded because of noncompliance, as these patients did not use the device at home as instructed. One patient was excluded because of pre-existing renal failure.

Of 16 patients who were included in the analysis, 10 patients received treatment and 6 received a non-healing light (placebo) treatment.

Of the 16 patients, 11 were male and 5 were female. In the placebo group 2 were female and 4 were male, whereas in the treatment group 5 were female and 11 were male. Average age was 62.9 years. It was 63.4 in the placebo group and 62.6 in the treatment group. Average BMI was 28.5, as expected from this study population. The average BMI of the treatment group was 30.4 while that of the placebo group was 25.3. The higher average BMI of the treatment group was a disadvantage for this patient group, because no offloading device was used in the study and therefore the treatment group patients on the average had more pressure on their leg ulcers.

All patients had diabetic ulcers, except 2 (from the treatment group) who had venous ulcers. Although venous leg ulcers and diabetic wounds have different pathology and etiology, in both cases lack of oxygen supply prevents healing. As light stimulates ROS-induced changes, which accelerate the mitochondrial respiratory chain, we were of the opinion that light treatment would affect both kinds of wounds in a similar way. In the placebo

![FIG. 2. Emission spectrum of the Vireo. Emission intensity is expressed in arbitrary units.](image-url)
group, 6 patients had 6 ulcers (one ulcer per patient). In the treatment group 10 patients had 19 ulcers (1.9 ulcers per patient) (Table 1).

When a patient suffered from more than one ulcer, wounds were considered “closed” when the last of the ulcers closed. Furthermore, the patient was invited to the clinic once more to verify that all ulcers were closed. If a patient exhibited a closed wound that remained closed for >1 month, no further treatment or follow up was performed. Photos of wounds before and after treatment are exhibited in Fig. 3. At the end of the follow up, all the wounds were closed in 9 out of 10 patients (90%) in the treatment group, whereas in the placebo group only 2 out of 6 patients presented closed wounds (33%), (2-tail p-value of Fisher test = 0.0357).

Mean follow-up time was 16.6 weeks, 17.8 in the placebo group and 15.9 in the treatment group. The average baseline area of ulcers per patient in the placebo group was 0.45 cm², whereas in the treatment group it was 1.08 cm² (average area of a single wound was 0.57 cm²). Baseline area was determined at the patient’s visit immediately before initiation of treatment. When the patient exhibited open wounds at the end of the study, the area of remaining open wounds per patient at the end of the treatment period was measured. This measurement was relevant to one patient in the treatment group and four in the placebo group. The average area of all remaining open ulcers was 0.12 and 0.21 cm² in the treatment and the placebo groups, respectively. The reduction in the wound size in the treatment group versus the placebo group was 89% versus 54%, respectively. The difference in percent reduction in wound size between treatment and placebo groups was statistically significant according to The Mann-Whitney U test (Tables 2 and 3). Figure 4 displays a graph that represents weekly average percentage of wound closure during the study, in the placebo and the treatment group. The percentage of wound closure was calculated according to wound measurements. If a patient failed to show up for a follow-up visit, the missing value of wound size was not entered into the calculation of average wound closure.

In the treatment group, median time to wound closure was 7.14 weeks and mean time was 11.16 weeks, whereas in placebo group mean and median time to wound closure was 11.5 weeks. Closure of wounds was verified for 1–6 weeks after the initial wound closure (mean time, 4.0 weeks) (Table 4).

### Table 1. Number of Wounds Treated

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>Treated</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of ulcers per patient</td>
<td>Mean 1.0</td>
<td>1.9</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Median 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Minimum 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Maximum 1</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Sum (total number of wounds treated)</td>
<td>6</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Std Deviation</td>
<td>0.00</td>
<td>1.60</td>
<td>1.31</td>
</tr>
<tr>
<td>Number of patients</td>
<td>6</td>
<td>10</td>
<td>16</td>
</tr>
</tbody>
</table>

### Table 2. Total Baseline Area in cm² of all Ulcers per Patient at the Beginning and the End of the Treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>Treated</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.45, 0.21</td>
<td>1.08, 0.12</td>
<td>0.85, 0.15</td>
</tr>
<tr>
<td>Median</td>
<td>0.17, 0.06</td>
<td>0.38, 0.00</td>
<td>0.27, 0.00</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.06, 0.00</td>
<td>0.12, 0.00</td>
<td>0.06, 0.00</td>
</tr>
<tr>
<td>Maximum</td>
<td>1.50, 1</td>
<td>4.08, 1</td>
<td>4.08, 1</td>
</tr>
</tbody>
</table>

As for safety parameters, there were no device-related adverse events.

### Discussion

The need to care for a population with chronic wounds is a growing challenge that requires innovative approaches. Two approaches that specifically address the identified pathophysiological processes involved in wound healing are hyperbaric oxygen therapy and light-based therapy. These two modalities are based on the same mechanism, i.e., ROS-induced changes in the redox state of the cell that are known to stimulate numerous intracellular signaling pathways,
regulate nucleic acid and protein synthesis, and activate enzymes and cell cycle progression. The results of these biochemical and cellular changes include benefits such as increased healing of chronic wounds.

Although several studies showed the efficacy of laser treatment to induce healing of skin wounds on the backs of rats, there are only few double-blind, placebo-controlled works supporting beneficial LEL treatment in humans with unhealed wounds.

Therefore, we decided to conduct a double-blind, placebo-controlled study in which we used a broadband light source in the visible and near IR range (400–800 nm), operating at 180 mW/cm², for treating patients with diabetic and venous ulcers. Unlike lasers in the visible range, which stimulate cell activity at a single wavelength, the present device provides a broad band of frequencies, which are more likely to be absorbed by cellular chromophores. Moreover, the broadband light device includes wavelengths in the blue region, which were found to induce greater cellular ROS than did red ones. Very recently, we also found blue light to be mostly responsible for NO formation by endothelial cells.

<table>
<thead>
<tr>
<th>Test statistics</th>
<th>Total area of all ulcers per patient at the beginning of the treatment</th>
<th>Total area of all ulcers per patient at the end of the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mann–Whitney U</td>
<td>22.500</td>
<td>15.000</td>
</tr>
<tr>
<td>Wilcoxon W</td>
<td>43.500</td>
<td>70.000</td>
</tr>
<tr>
<td>Z</td>
<td>−.815</td>
<td>−1.978</td>
</tr>
<tr>
<td>Asymp. sig. (2-tailed)</td>
<td>0.415</td>
<td>0.048</td>
</tr>
<tr>
<td>Exact sig. [2*(1-tailed sig.)]</td>
<td>0.428² (Not corrected for ties. Grouping variable: group.)</td>
<td>0.118² (Not corrected for ties. Grouping variable: group.)</td>
</tr>
</tbody>
</table>

FIG. 4. The average percentage of wound closure as a function of the study duration (in weeks).
microcirculatory blood flow, the use of visible light containing wavelengths in the blue region might be of great importance for wound healing of diabetic and venous ulcers. It is true that the penetration of blue light into the tissue is limited, but for wound healing no deep penetration is required.

Our small-scale double-blind controlled study supports the promise of broadband light therapy including blue wavelengths. At the end of the follow up, the treatment group demonstrated a high wound closure rate, 90% of treated patients, versus 33% of the placebo group; and high wound area reduction, 89% versus 54% of the placebo group. However, large-scale studies are still required. A final advantage of this approach is that light treatments are painless, and no adverse effects have ever been reported.

## Acknowledgment

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## Author Disclosure Statement

Rachel Lubart is the scientific advisor of Qray.

## References


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### Table 4. Time to Wound Closure in Treatment and Control Groups—Weeks from First Visit

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>Treated</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to wound closure in weeks (average per patient)</td>
<td>Mean 11.50</td>
<td>11.16</td>
<td>11.23</td>
</tr>
<tr>
<td></td>
<td>Median 11.50</td>
<td>7.14</td>
<td>8.86</td>
</tr>
<tr>
<td></td>
<td>Minimum 8.86</td>
<td>3.00</td>
<td>3.00</td>
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<tr>
<td></td>
<td>Maximum 14.14</td>
<td>23.00</td>
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<tr>
<td>Valid N</td>
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<td>9</td>
<td>11</td>
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