Phototherapy Improves Healing of Chronic Venous Ulcers

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Abstract

Objective: We tested the hypothesis that LED phototherapy with combined 660-nm and 890-nm light will promote healing of venous ulcers that failed to respond to other forms of treatment. Background Data: A variety of dressings, growth factors, and adjunct therapies are used to treat venous ulcers, but none seems to yield satisfactory results. Materials and Methods: We used a randomized placebo-controlled double-blind study to compare a total of 20 patients divided with 32 chronic ulcers into three groups. In group 1 the ulcers were cleaned, dressed with 1% silver sulfadiazine (SDZ) cream, and treated with placebo phototherapy (<.03 J/cm²) using a Dynatron Solaris 705 phototherapy research device. In group 2 the ulcers were treated similarly but received real phototherapy (3 J/cm²) instead of placebo. In group 3 (controls), the ulcers were simply cleaned and dressed with SDZ without phototherapy. The ulcers were evaluated with digital photography and computer image analysis over 90 d or until full healing was attained. Results: Ulcers treated with phototherapy healed significantly faster than controls when compared at day 30 (p<0.01), day 60 (p<0.05), and day 90 (p<0.001), and similarly healed faster than the placebo-treated ulcers at days 30 and 90 (p<0.01), but not at day 60. The beneficial effect of phototherapy was more pronounced when the confounding effect of small-sized ulcers was removed from the analysis. Medium- and large-sized ulcers healed significantly faster with treatment (≥40% rate of healing per month) than placebo or control ulcers (p<0.05). Conclusion: Phototherapy promotes healing of chronic venous ulcers, particularly large recalcitrant ulcers that do not respond to conventional treatment.

Introduction

Leg ulcers are characterized by circumscribed or irregular loss of the epidermis and possibly the dermis and subcutaneous tissues of the lower limbs.¹ They vary in etiology but generally include venous ulcers, arterial ulcers, pressure ulcers, diabetic ulcers, anemic ulcers, and ulcers associated with autoimmune diseases, among others.² Venous ulcers, the most common form of leg ulcers accounting for 75% of cases, result from chronic insufficiency of venous return due to abnormal functioning of the network of superficial and deep veins.³-⁴

Regular topical dressing is the most common form of treatment for venous ulcers. Dressing with 1% silver sulfadiazine (SDZ) has been used to treat venous ulcers, pressure ulcers,⁵-⁸ and burns⁹ for more than 30 y because of its potential antimicrobial activity.¹ Because of lackluster response to SDZ and other chemical interventions such as growth hormones, interest in other forms of treatment that may accelerate healing of venous ulcers has been high. Phototherapy with 600- to 1000-nm laser or light-emitting diode (LED) sources of light have been shown to promote tissue repair in experimental and clinical cases of wound healing, including burns.¹⁰-¹⁴

Evidence indicates that phototherapy promotes local blood flow, stimulates the proliferation of cells, including epithelial and endothelial cells, keratinocytes, macrophages, lymphocytes, and fibroblasts, and increases collagen synthesis as well.¹⁵-¹⁶ Others have shown that phototherapy with lasers, LEDs, or superluminous diodes (SLDs) accelerates inflammation,¹⁷ promotes fibroblast proliferation,¹⁸-¹⁹ increases chondroplasia²⁰ and collagen synthesis,¹⁵,²¹-²²

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stimulates bone repair and remodeling,\textsuperscript{23–24} increases the vascularization of skin wounds,\textsuperscript{25} and accelerates tissue repair in a variety of experimental models.\textsuperscript{26–28}

However, treatment parameters, such as duration of treatment, irradiance, fluence, and frequency of treatment, differ significantly from one study to another, creating mixed results and skepticism about the clinical value of phototherapy. The level of skepticism is further heightened by the increasing use of newer less coherent LED devices instead of lasers, which are familiar, well-studied, and unique for their coherent light properties. LED-based devices offer some advantages; they are relatively less expensive, easily configured, and economically permit the emission of two or more wavelengths of light in a single applicator or probe that may vary in size. Although fewer studies have examined the clinical efficacy of these multi-wavelength devices, available data suggest that they also promote tissue repair.

Treatment of venous ulcers will be significantly improved if indeed phototherapy with one or more wavelengths of light in the 600- to 1000-nm range promotes tissue repair. Consequently, we used a randomized placebo-controlled double-blind study to test the hypothesis that a combination of visible 660-nm and invisible 890-nm light will promote healing of chronic venous ulcers, in particular indolent ulcers that were not responding to any other form of treatment.

Materials and Methods

Patients

Twenty patients with 32 chronic venous ulcers who met the following inclusion criteria were recruited into the study following approval by the Research Ethics Committee of the Teaching Health Center, Faculty of Medicine, University of São Paulo, Ribeirão Preto, Brazil (protocol no. 0175, March 14, 2006): (1) presence of an ulcer in the lower extremity, (2) ulcers larger than 1.0 cm\textsuperscript{2}, (3) ulcer duration $\geq$ 6 wk, (4) presence of classical signs of venous insufficiency such as edema, varicosities, lipodermatosclerosis, eczema, and elephantiasis nostra, (5) controlled systemic arterial hypertension (diastolic arterial pressure $< 95$ mm Hg), and (6) voluntary submission of a written signed informed consent to participate in the study. Every patient was seen and treated at the Ulcer Outpatient Clinic of the Teaching Health Center, Faculty of Medicine, University of São Paulo, Ribeirão Preto, Brazil.

The patients were randomly assigned to three groups and followed for as long as 90 d. Each group of ulcers was treated twice per week. Ulcers were covered with 1\% silver sulfadiazine (SDZ) cream, dressed, and then bandaged. In addition to this standard ulcer care, the 11 ulcers assigned to group 1 (G1) received placebo phototherapy using Probe One, while the 14 ulcers of group 2 (G2) were treated with Probe Two. The control group 3 (G3) had seven ulcers that received standard care without phototherapy.

Phototherapy equipment

The patients were treated with a Dynatron Solaris 705\textsuperscript{\textregistered} phototherapy research device (DynaTronics Corporation, Salt Lake City, UT, USA), specially designed to permit double-blind study. The machine was equipped with two identical interchangeable probes labeled “one” and “two.” Aside from the emission of similarly colored red light, no other parameters of the light produced by the two probes was known to the investigators until the study was completed. To further promote the anonymity of treatment parameters, no contact was made with the manufacturer until the study was completed. The characteristics of the two probes, which were revealed after the study was completed, indicated the following: Probe Two was designed to emit the full complement of 500-mW light from 36 diodes interspersed in a 5-cm\textsuperscript{2} cluster—32 15-mW 890-nm SLDs and four 5-mW 660-nm SLDs. Since 660-nm light is visible red light, and 890-nm light is invisible, the 890-nm SLDs in Probe One were disabled so that it produced only 660-nm light. To further reduce the amount of light emitted by the probe, the outer three diodes were also disabled so that only the centrally located red diode produced light. In addition, a resistor was added to the circuit to further reduce the amount of light emitted by the diode. Thus, Probe One as a placebo control treatment applicator delivered less than 5 mW of red light, while Probe Two served as the real treatment applicator (Fig. 1). Fitted with the real applicator (Probe Two), the Dynatron Solaris 705 device has an irradiance of 100 mW cm\textsuperscript{-2}, and with the placebo applicator Probe One, the irradiance is less than 1 mW cm\textsuperscript{-2}.

Treatment

After cleaning each ulcer with physiological saline, the ulcers of group 2 were covered with a transparent plastic protective cover; then phototherapy was applied to one 5-cm\textsuperscript{-2}
area at a time for 30 sec per point, until the entire ulcer surface was treated with the probe. Therefore the total duration of treatment varied in direct proportion to the size of each ulcer.

**Ulcer measurement**

Photographs of each ulcer were taken with a Sony-DSC P93 digital camera (Sony USA, New York, NY USA) every 15 d. Image capture was standardized using an 80-cm-high arc-shaped aluminum support to which the camera was fixed perpendicularly to the ulcer. A self-adhesive label with a ruler that was photographed with each ulcer, and thus the area of granulation and sphacelus tissue. The ratios of different types of tissue, such as granulation tissue and fibrin or sphacelus tissue, within the ulcer bed based on the color classification of Fowler et al.: red for granulation tissue and yellow for devitalized tissue (fibrin or sphacelus). The computer automatically calculated the area of each ulcer as well as the area of granulation and sphacelus tissue. The ratios of the different types of tissue were computed using the scale of the ruler that was photographed with each ulcer, and thus the ulcer healing rate (UHR) was calculated (initial area \([A_i]\) minus the final area \([A_f]\) divided by the initial area \([A_i]\)). This index permits the assessment of ulcer re-epithelialization.

**Statistical analysis**

The mixed effects test (modified ANOVA) was used for comparative statistical analysis of the groups, and for detecting the effect of treatment on ulcer area, since some of the patients had more than one ulcer and the independence of individual observations cannot be assumed. Furthermore, the proportion of ulcers in each group that healed significantly (i.e., ≥40% rate of healing) were similarly compared. The level of significance was set at \(p < 0.05\).

**Results**

Clearly visible clinical signs associated with the ulcers at the beginning of treatment were: hyperchromia (69%), lipo-dermatosclerosis (60%), varicosity (85%), edema (69%), pruritus (32%), eczema (50%), and pain (82%).

As shown in Table 1, the three groups of ulcers were well matched in terms of their clinical and general characteristics.

Table 1. Clinical Characteristics of the Patients by Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (placebo)</th>
<th>Group 2 (Real treatment)</th>
<th>Group 3 (control)</th>
</tr>
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<tbody>
<tr>
<td>Number of ulcers</td>
<td>11</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Duration of ulcer (mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>164.2 ± 69.5</td>
<td>114.2 ± 64.1</td>
<td>112.0 ± 45.2</td>
</tr>
<tr>
<td>Median</td>
<td>154.1</td>
<td>114.2</td>
<td>116.0</td>
</tr>
<tr>
<td>Range</td>
<td>24–240</td>
<td>36–240</td>
<td>12–240</td>
</tr>
<tr>
<td>Initial ulcer size in cm² (mean ± SD)</td>
<td>15.2 ± 9.2</td>
<td>21.9 ± 21.4</td>
<td>25.6 ± 13.8</td>
</tr>
</tbody>
</table>

**Discussion**

Finding a way to heal chronic venous ulcers remains a conundrum in clinical practice. Standard treatments seem ineffective, and reduce the quality of life of most patients. In the last 20 y, new treatment procedures have been developed and tested, resulting in minimal improvements to previously available treatment options, prompting this randomized double-blind placebo-controlled clinical study designed to determine the efficacy of phototherapy when used in combination with standard daily treatment with 1% SDZ cream dressing.

The ulcers in each of the three groups varied in duration...
and size, as evidenced by the standard deviations shown in Table 1. This reflects the clinical variety of the patients seen at the clinic. Whereas the initial sizes of the ulcers did not differ statistically significantly, our results showed that—at all time points—the ulcers treated with the full dose of 660-nm and 890-nm light healed faster than the control group treated with SDZ cream dressing alone, as well as the placebo treatment group, when compared at days 30 and 90. This finding is consistent with the results obtained in studies using 600- to 1000-nm wavelengths of coherent or non-coherent light in experimental and clinical investigations of tissue repair. In a retrospective study of 42 patients with venous leg ulcers, Kleinman et al. reported full gran- 
ulation and closure of ulcers in a total of 36 patients (87.5%) who were treated with either a 785-nm scanning laser source or a laser scanner with combined 632.8-nm and 765-nm light. Similarly to our study, the duration of treatment was 3.5 ± 0.66 mo. In a similarly uncontrolled study of 62 patients with chronic venous leg ulcers that had not responded to therapy for at least 6 mo, Lichtenstein and Morag found that treatment with either a 632.8-nm red laser or an 830-nm infrared light source resulted in complete wound healing in 53 (85.48%) of the patients during a 2- to 14-wk treatment period. The ulcers of four more patients improved significantly during the same period, and no adverse effects were reported by the patients. Consistent with our findings, a low energy density was used to accomplish their results. Others have shown that similarly low amounts of red and/or infrared light promote healing of diabetic ulcers, venous ulcers, and decubitus ulcers, but there are indications that

<table>
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<tr>
<th>Group</th>
<th>Mean ulcer healing rate (%)</th>
<th>Median ulcer healing rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 d</td>
<td>60 d</td>
</tr>
<tr>
<td>Group 1 (placebo)</td>
<td>20 ± 0.20</td>
<td>30 ± 0.20</td>
</tr>
<tr>
<td>Group 2 (treatment)</td>
<td>30 ± 0.23</td>
<td>40 ± 0.25</td>
</tr>
<tr>
<td>Group 3 (control)</td>
<td>−10 ± 0.38</td>
<td>10 ± 0.29</td>
</tr>
</tbody>
</table>

FIG. 2. Representative images of the ulcers. A1–A4 are group 1 ulcers, while B1–B4 and C1–C4 are from groups 2 and 3, respectively, seen here at various stages of healing. The numbers correspond to the number of days posttreatment: A1 corresponds to day zero, and A2, A3, and A4 correspond to days 30, 60, and 90, respectively.
phototherapy does not accelerate healing of second- and third-degree burns in rats, even though it has bactericidal and histological effects on such burns.\textsuperscript{52,53}

Placebo ulcers treated with ultra-low doses of red 660-nm light—a treatment that we thought would be ineffective—healed faster at day 90 but not at days 30 or 60 when compared to control ulcers that did not receive phototherapy at all. This finding suggests that the cumulative amount of energy applied to an ulcer over a long time period matters, not just the energy fluence used at each session. Ultra-low doses applied over a long period may produce the same effect as higher doses used over a shorter period of time. Our findings suggest that the effect of our placebo treatment would have been masked if treatment had been limited to 30 or 60 d, and not extended to 90 d. Nonetheless, the superior effect of real treatment was clearly evident at all time intervals, particularly when larger ulcers were analyzed separately.

Seven of the ulcers treated in our study were relatively small in size, and they healed fully within 60 d whether or not they were treated with light. Only with phototherapy did any significant healing occur in the remaining 25 medium- to large-sized ulcers. This finding underscores the clinical value of phototherapy in treating ulcers that do not respond to other forms of therapy. The phototherapy literature is often perceived to be replete with contradictory data. Therefore, a brief comment seems warranted considering this aspect of our results, even though others have offered detailed comments and analysis of the literature in the past.\textsuperscript{54–57}

Lagan et al.\textsuperscript{58} used 830-nm light to treat nine patients with 12 “minor postsurgical wounds” using 300 mW cm\textsuperscript{-2} irradiance and 9 J/cm\textsuperscript{2} fluence; they found no difference in wound closure and no difference in pain levels between patients in the treatment group and controls. Our finding that small-sized ulcers or minor wounds tend to heal properly regardless of phototherapy support their results. Under normal circumstances, regular treatment with light would not produce a significant difference in the mean healing rate of such minor wounds. In other words, it may not be necessary to treat such wounds with light. Barring infection, surgical wounds heal within days when dressed regularly. But it should be noted that Rezende et al.\textsuperscript{59} showed that treating such wounds once with 1.3 J/cm\textsuperscript{2} of 830-nm light resulted in faster healing, suggesting that a different phototherapy treatment protocol may be needed to accelerate healing of surgical incisions.

<table>
<thead>
<tr>
<th>Category of ulcer</th>
<th>Group 1 (30 d, 60 d, 90 d)</th>
<th>Group 2 (30 d, 60 d, 90 d)</th>
<th>Group 3 (30 d, 60 d, 90 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small (&lt;5 cm\textsuperscript{2})</td>
<td>33, 100, 100</td>
<td>100, 100, 100</td>
<td>100, 100, 100</td>
</tr>
<tr>
<td>Medium (5–10 cm\textsuperscript{2})</td>
<td>0, 3, 3</td>
<td>75, 50, 75</td>
<td>0, 0, 0</td>
</tr>
<tr>
<td>Large (&gt;10 cm\textsuperscript{2})</td>
<td>0, 20, 20</td>
<td>0, 43, 57</td>
<td>0, 0, 0</td>
</tr>
</tbody>
</table>

**FIG. 3.** A box plot comparison of the wound healing rates (WHR) of the three groups at 30, 60, and 90 d of treatment. WHR is shown in figures that when multiplied by 100 give the percentage rate of healing. Time and group are shown on the x-axis. Whereas the group 2 ulcers treated with real phototherapy showed signs of healing at every time point, some of the ulcers in the placebo group and most of the ulcers in the control group became worse over time. *Difference between group and group 2 at each time point; **difference between group and groups 1 and 2 at each time point.
Similarly, Franek et al. 50 studied 65 patients with leg ulcers in three groups over an average of 4.5 wk. In addition to phototherapy, one group of 21 patients received 810-nm phototherapy 5 d/wk at 4 J/cm², while the second group received sham phototherapy and dressing, and the ulcers in the third group were simply dressed, thus serving as controls. They found no statistically significant impact of laser light on any of the stages of healing. Our experience with wound healing in a rat model of diabetic ulcers suggests that treatment of such ulcers should be limited to two to three times per week at most, not five times per week, because of the tendency to stimulate collagen synthesis progressively, without allowing an interval for newly synthesized collagen to undergo maturation. 22,26,61

Our results revealed the superior healing effects of real phototherapy versus placebo light, particularly when, in keeping with some of the observations of Steed et al., 62 without allowing an interval for newly synthesized collagen to undergo maturation. 22,26,61

Our results revealed the superior healing effects of real phototherapy versus placebo light, particularly when, in keeping with some of the observations of Steed et al., 62 smaller-sized ulcers were excluded from the data. Because small venous ulcers may heal on their own and medium to large ulcers often do not, our findings strengthen the view that the real value of phototherapy lies in the treatment of indolent recalcitrant ulcers that are generally unresponsive to conventional therapies. It is not surprising therefore, that attempts to compare phototherapy with standard wound care of surgical incisions or minor ulcers failed to reveal the superior healing effects of light therapy in such circumstances.

According to the Guidance for Industry, 35 an ultimate goal in clinical studies is to achieve total wound closure without recurrence and without drainage or the need for dressings. Clinical results depend on the physiopathology and the size and duration of the ulcers. Some ulcers may not close completely during the usual 12- to 14-wk period of most clinical investigations. 36 Therefore, there is a need to study a larger sample and to follow-up with patients after 90 d, or after the wounds have closed, in order to monitor the potential for ulcer recurrence. Therein lies a limitation of our study.

Conclusion

We conclude that phototherapy accelerates the healing process of chronic venous ulcers compared to regular dressing with 1% silver sulfadiazine cream alone or placebo light therapy. Further study with a larger sample size and longer posttreatment patient follow-up is recommended.

Disclosure Statement

No conflicting financial interests exist.

References


