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Effect of Visible and Infrared Photobiomodulation on Diabetic Foot Ulcers

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Abstract

Introduction: Diabetes is a highly prevalent disease worldwide. Despite routine treatments, there is no effective treatment approach for patients with diabetic foot ulcers (DFUs). A new approach to reduce complications and control DFU is low-level laser therapy (LLLT). In the present study, we evaluated the therapeutic effects of LLLT on the symptoms of DFU patients.

Methods: Sixty diabetic patients with DFU were included in this randomized clinical trial and were randomly allocated into two groups of laser (n = 30) and control (n = 30) with signed written consent. The LLLT group underwent visible and infra-red laser therapy and conventional medical treatment, while the control group received only conventional medical treatment. The total laser irradiation sessions of the patients were 20 sessions, (three sessions a week) and each session lasted for 30 minutes over the entire surface of the wound. The power density per session for each laser was calculated to be 35.65 mW/cm^2 with an energy density of 64.17 J/cm^2.

Results: The mean area of ulcers in the LLLT group reduced significantly ($P < 0.001$) from 441.7 ± 365.5 mm^2 before LLLT to 163.9 ± 213.9 mm^2 from the baseline up to the last session of LLLT, indicating a 62.99% reduction in mean ulcer area. In the control group, the mean ulcer area did not change significantly. Wagner's classification of the patients in the LLLT group reduced to lower grades significantly ($P < 0.01$), while the classification moved towards higher grades in the control group ($P < 0.08$).

Conclusion: In this study, we showed the effectiveness of LLLT in the reduction of the surface and depth of DFUs. The results documented that patients experienced significant improvements in the healing of their foot ulcers after laser therapy. It is recommended that the LLLT be considered as a non-invasive method for the treatment of DFU patients.

Keywords: Diabetic foot ulcers; Low level laser therapy; LLLT; Wagner classification.

Introduction

Diabetes is a widespread disease with a serious impact on patients' quality of life, and its estimated prevalence is about 371 million people worldwide.[1,2] Distal sensorimotor neuropathy may occur in 50% of diabetic patients.[2] One of the most serious complications of neuropathy is diabetic foot ulcer (DFU), which is due to abnormal foot biomechanics and antipathy of peripheral vessels and reduced pressure and pain sensation. The usual treatment for this condition includes controlled hyperglycemia, wound debridement, antibiotic treatment, and complete leg cast. DFU usually appears as a chronic skin ulcer without healing on the lower extremity of the patients.[3] DFU, as one of the causes of limb amputation, can be considered an effective factor that deteriorates diabetic patients`quality of life.[4,5] Despite routine treatments in clinics, there is no effective treatment approach for DFU patients.[6-13] low-level laser therapy (LLLT)which is also known as photobiomodulation using low-power lasers is considered as a new effective method for treating DFU.

It has been reported that the laser beam absorption in cell chromophores such as cytochrome C oxidase (CCO) plays an important role in increasing ATP production.[14] CCO has specific absorption peaks in the red (~630 nm) and near-infrared (~800 nm) spectral regions, and as a result, the most commonly used wavelengths in LLLT are in these two regions of the spectrum.

There is a lot of evidence showing the biological effectiveness of LLLT, including anti-inflammatory properties, wound healing, and pain relief.[14,15] It is also reported that LLLT could promote fibroblast proliferation, repair in injured neurons, and neurogenesis.[6-15]

Several clinical studies have shown the effectiveness of the LLLT in the healing of DFUs with no observed side effects.[16,17] While LLLT effects have been reported with visible lasers in the red spectrum (600-700 nm) or near-infrared (780-980 nm) lasers, there is insufficient information on the combined effect of visible and infrared lasers on the DFU patients.

Therefore, in this study, we investigated the simultaneous effects of two laser beams with wavelengths of 630 nm and 810 nm on diabetic foot wound healing.

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Patients and Methods

Patients and Groups

Sixty type 2 diabetic patients with a history of DFU were enrolled in this randomized controlled study. After a trained physician provided explanations to the patients participating in this, written informed consent was obtained from the patients. Patient information including age, sex, hand and foot anesthesia, and duration of diabetes was recorded. Diabetic patients with DFU were included in this randomized clinical trial and were randomly allocated into two groups of laser (n = 30) and control (n = 30) with signed written consent. The LLLT group underwent laser therapy and conventional medical treatment, while the control group received only conventional medical treatment. The conventional medication included tight diabetic mellitus (DM) with oral medication or insulin therapy, antibiotic therapy, and debridement of ulcers as indicated. In both groups, a removable cast walker was used as an offloading device.

Low-Level Laser Therapy

All patients in the LLLT group underwent laser therapy with two wavelengths of 630 and 810 nm. Both lasers were set in pulsed mode with a frequency of 35 Hz, an average power of 7 mW and a spot diameter of 5 mm. The total number of laser irradiation sessions for the patients was 20 sessions, (three sessions per week), and each session lasted 30 minutes. Laser irradiation was performed uniformly on the entire area of the wound surface. The power density in each session for each laser was calculated to be 35.65 mW/cm^2 with an energy density of 64.17 J/cm^2.

Evaluation and Classification of Diabetic Foot Ulcers

The diameter and depth of the wounds of the patients in both groups were measured with a suitable sterile ruler, and the wound surface was calculated. Patients' wounds were classified at the beginning and at the end of the last laser treatment session using Wagner's DFU classification system. In this classification system, DFU patients are classified into six grades from 0 to five. Grade 0 indicates healthy skin, while Grade 1 indicates the presence of a superficial wound. Grade 2 indicates the presence of deep wounds in patients, while in grade 3 patients, wounds with osteomyelitis are observed. The last two groups (4 and 5) indicate serious complications in the patients' ulcers, so grades 4 and 5 indicate the presence of partial and complete gangrene of the foot, respectively.

Data Analysis

SPSS version 20 software was used for data analysis. In order to evaluate the normal distribution of the data, the Kolmogorov-Smirnov test was used. The paired *t* test was also used to evaluate the difference between the groups.

Results

Table 1 shows the demographic data of the patients. By comparing the two groups of control and laser therapy, the parameters of mean age, sex, frequency of nephropathy, HbA1C and insulin count, no significant difference was observed between the two groups ($P > 0.05$). Among all patients participating in the study, the female to male ratio was 0.81. The average age of the patients in the control group was 58.4 years, and it was 59.7 years in the LLLT group. The prevalence of neuropathy in the control and LLLT groups was 80.0% and 93.3%, respectively, with no significant difference ($P > 0.05$).

Figure 1 shows the photographs of the chronic wounds of three patients before and after LLLT, demonstrating

Table 1. Demographic Characteristics of Patients in LLLT and Control Groups

Variable		LLLT Group (Mean ± SD)	Control Group (Mean ± SD)
Number of observations		30	30
Age		59.7 ± 9	58.4 ± 11.5
Gender	Male	16(53.3%)	17 (56.6%)
	Female	14 (46.7%)	13 (43.4%)
Diabetic neuropathy		28 (93.3%)	24 (80%)
HbA_1C		9.53 ± 9	8.73 ± 1.50
Insulin No. (%)		12 (40.0%)	11 (36.7%)

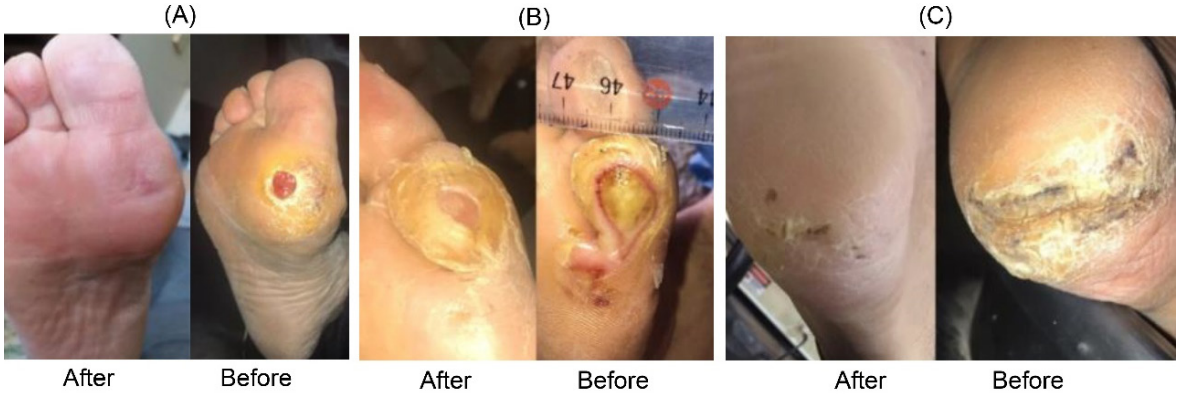

Figure 1. Photographs of the Wounds of Three Patients Before and After LLLT. (A) 65 Years old female patient with 10 years history of diabetes, (B) 50 years old male patient with 10 years history of diabetes, and uncontrolled FBS, and (C) 53 years old male patient with 6 years history of diabetes and uncontrolled FBS

the considerable healing or complete enclosure of the ulcers. After 20 successive LLLT treatment trials, one patient (3.57%) from the LLLT group and no patient from the control group had complete wound closure. Figure 2 shows the mean ulcer area in patients of LLLT and control groups before and after the last session of LLLT. The independent samples t test showed no significant difference between LLLT and control groups before the intervention ($P > 0.05$). The mean area of ulcers in the LLLT group reduced significantly ($P < 0.05$) from 441.7 ± 365.5 mm^2 before LLLT to 163.9 ± 213.9 mm^2 after the last session of LLLT, indicating the positive effect of LLLT on wound healing with a 62.99% mean reduction in the ulcer area. On the other hand, in the control group, there was no significant difference between the mean ulcer area from the baseline up to the end of the study.

Figure 3 shows the mean ulcer depth in LLLT and control groups before and after LLLT. The mean depth of ulcers in the LLLT group reduced significantly ($P < 0.05$) from 5.75 ± 2.66 mm before LLLT to 2.55 ± 1.92 mm after the last session of LLLT, with a 55.6% mean reduction in the ulcer depth. There was also no significant difference between the mean ulcer area of patients in the control group from the baseline up to the end of the study.

The Wagner classification of the patients is shown in Figure 4 for LLLT (left) and control groups (right). In the LLLT group, the classification of the patients was changed significantly to lower grades ($P < 0.05$), while the classification moved towards higher grades in the control group ($P < 0.05$).

Discussion

DFUs remain a major therapeutic challenge in clinics with a lack of effective treatment. Among the routine methods for treating DFUs, LLLT is considered a non-invasive and non-pharmacological method for treating DFUs with no side effects. There are several studies addressing the wound repair mechanisms of LLLT such as, faster cell proliferation, fibroblast cell growth, cellular migration to the wound site, anti-inflammatory effects, and more formation of connective tissue in laser irradiated wounds.[18-28]

Several articles have reported the effectiveness of LLLT for treating diabetic wounds by choosing different treatment protocols. The parameters of the protocols used in various studies are laser wavelength, laser irradiation

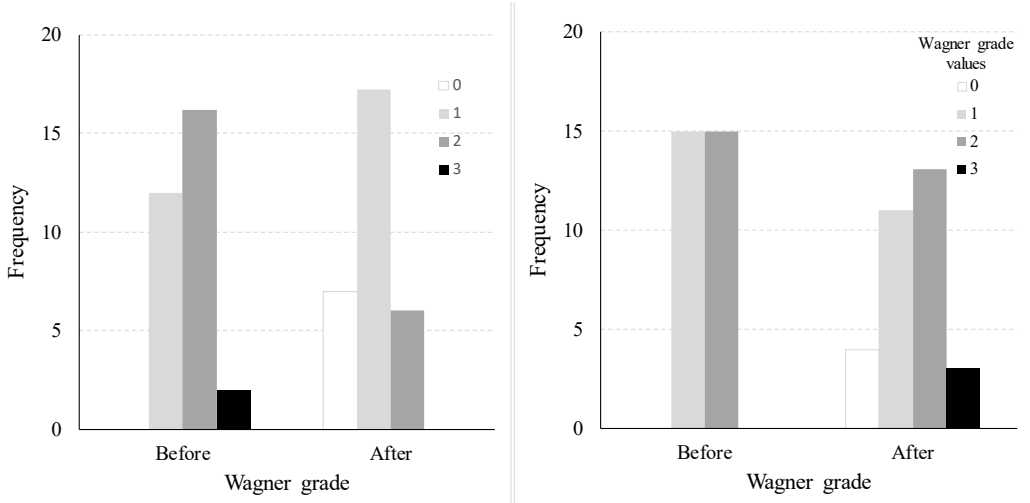

Figure 2. Changes in Wagner Classification of Patients' Ulcers in LLLT (Left) and Control (Right) Before and After Intervention

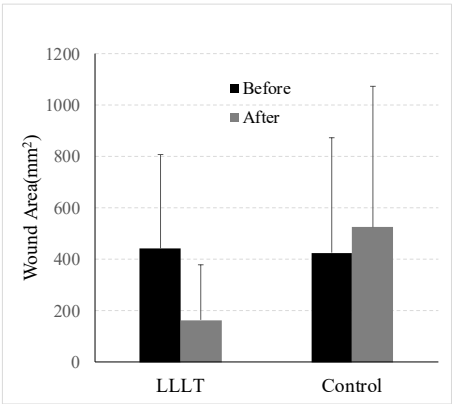

Figure 3. Variation of Ulcer Area in LLLT and Control Groups

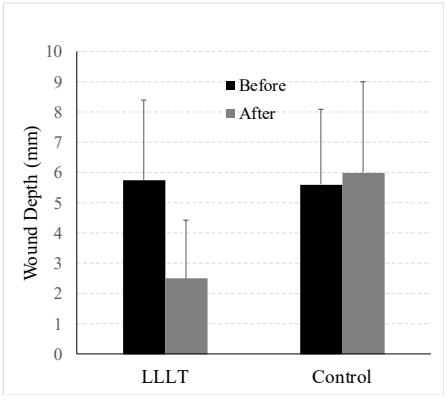

Figure 4. Variation of Ulcer Depth in LLLT and Control Groups

time, energy density, and the number of laser radiation sessions. Two important parameters of the LLLT treatment protocols used are the laser wavelength and energy density. The wavelengths used in different studies range from 600-950 nm, which is also known as the therapeutic window. A group of clinical trial studies used the visible lasers for LLLT with a fluence or energy density span of 3-35 J/cm^2 and treatment time span of 0.32-20 minutes, and the number of sessions was in the range of 12-80. The main outcomes of these studies were the faster healing of wounds and a considerable decrease in the size of the wounds and pain in the LLLT group in comparison with the control group.[29-34] There is also another group of clinical trial studies that have used the near infra-red lasers with an energy density span of 1.5-6 J/cm^2, treatment time span of 0.5-10 minutes, and the number of sessions was in the range of 26-48.[35,36] The outcomes of these studies were almost similar to those using visible lasers.

There is a lot of literature supporting the use of a combination of two visible and near infra-red wavelengths for the effectiveness of LLLT in the treatment of DFU patients.[37-39] The mechanisms of action of LLLT have been discussed through many studies. At the cellular level, it is reported that LLLT increases the adenosine triphosphate level as well as oxygen consumption by the cells, initiating the healing effects of LLLT in the biological system.[34,35] It has been proved that CCO has absorption peaks in the red region of light spectra (≈630 nm) and near the infra-red region (≈800 nm).

There were two studies employing a combination of two visible and infrared wavelengths for the treatment of DFU patients.[40,41] A randomized placebo controlled study used 660 and 890 nm LEDs for treating DFU patients. The energy densities were < 1 J/cm^2 and 3 J/cm^2 for placebo and treatment groups, respectively. Thirty days after laser therapy, the treatment group had 79.2% faster healing in comparison with the placebo group [40]. In a case series study, a combination of 660 nm 1.5 J/cm^2 and 980 nm 6 J/cm^2 lasers was used for treating DFU patients. After 18 sessions of applying LLLT on 30 patients with DFUs, the ulcer area and the grade of ulcers decreased significantly.[41]

Therefore, in the present study, we chose two laser beams with wavelengths of 630 and 810 nm in order to obtain better therapeutic results in the treatment of DFU patients. Our results are in agreement with studies using two visible and near infra-red lasers.[40,41]

Conclusion

This study clearly proved that the use of LLLT with the combination of visible and infrared laser beams can be effective in healing the wounds of diabetic patients. In this study, two considerable results are significant. First, the surface and depth of the wounds decreased in the laser treatment group and increased in the control group. Second, in the LLLT group, Wagner's classification of ulcers changed to lower grades, while in the control group, it changed to higher grades. As a conclusion, photobiomodulation or LLLT with two visible and infrared laser beams, can be used as an effective non-invasive treatment method in the treatment of the chronic wounds of diabetic patients without side effects. On the other hand, considering the low efficiency of routine treatment methods for treating diabetic ulcers, this method can be used as an auxiliary treatment to increase the efficiency of conventional treatment methods for DFU patients.

Authors' Contribution

Conceptualization: Faraj Tabeie, Alireza Ebadi.
Data curation: Sara Tabakhha.
Formal analysis: Faraj Tabeie, Sara Tabakhha.
Funding acquisition: Faraj Tabeie, Alireza Ebadi.
Investigation: Faraj Tabeie, Alireza Ebadi, Sara Tabakhha.
Methodology: Faraj Tabeie, Soheila Sadeghi.
Project administration: Faraj Tabeie, Alireza Ebadi.
Resources: Faraj Tabeie, Alireza Ebadi.
Software: Soheila Sadeghi.
Supervision: Faraj Tabeie.
Validation: Faraj Tabeie, Alireza Ebadi.
Visualization: Faraj Tabeie, Sara Tabakhha.
Writing–original draft: Sara Tabakhha.
Writing–review &editing: Faraj Tabeie.

Competing Interests

None.

Ethical Approval

This project was approved by Shahid Beheshti University of Medical Sciences with the ethical code of IR.SBMU.MSP.REC.1398.275.

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