RESEARCH PAPER

Efficacy of Photobiomodulation on Wound Healing and Interleukin 6 in Neuropathic Foot Ulcer

Fatma M Abdallah [1], Amal M Abd Elbaky [1], Amr A Gomaa[2], Hussein G Mogahed[1]

1. Department of Physical Therapy for Surgery, Faculty of Physical Therapy. Cairo University, Egypt.
2. Department of Plastic Surgery, Faculty of Medicine, Suez Canal University, Egypt.

ABSTRACT

Background: Diabetic neuropathy, which causes chronic ulcers of the lower limb that do not heal, continues to be a worldwide problem in public health.

Methods: Sixty-eight patients with neuropathic foot ulcer from both sexes took-part in this study, aged between 50 to 70 years. They were selected and divided randomized two equivalent groups (n=34). Patients took 4 weeks treatment sessions. Group A received He-Ne-low level laser therapy sessions /week for 20 minutes plus conventional treatment as in group B. Group B received conventional treatment of wound. All outcome variables were measured before and after treatment program (wound size by Imito measure application, Interlukin-6 level measured with blood sample test).

Results: The results revealed a significant reduction wound surface area and Interleukin 6 (p=0.001) in both groups post treatments in the favour of group A.

Conclusion: Adding photobiomodulation to conservative treatment was very effective on wound healing along with Interleukin 6 in patients with neuropathic foot ulcer.

Keywords: Interleukin 6, Neuropathic Foot Ulcer, Photobiomodulation, Wound Healing.

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INTRODUCTION

Type II diabetes mellitus (DM) refers to a chronic disease marked by high blood glucose levels and higher cellular insulin resistance, along with a gradual decrease in insulin release. Nerve damage in the legs, which can lead to ulcers and even amputations, is a common complication of diabetes. This condition can develop for a variety of reasons, including increased plantar pressure, vascular impairment, traumatic conditions, as well as diabetic peripheral neuropathy [1].

Diabetes-related peripheral neuropathy and vascular disease are the main causes of diabetic foot, which results in ulcers on the feet. Infection and/or soft tissue loss can spread from this ulceration, leading to impaired walking and a significant impact on quality of life [2]. There is a significant rate of morbidity and mortality that are linked with neuropathic foot ulcers, which are among the most aggressive and costly consequences of diabetic foot. It has been estimated that an ulcer will develop on the foot or ankle of 15% of people with DM during their lifetime [3].

Hyperglycemia causes oxidative stress by disrupting the balance of free-radical-generating as well as free-radical-scavenging mechanisms. Damage to live cells and tissues can occur as a result of oxidative stress, which free radicals cause [4]. The release of proinflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8, along with tumour necrosis factor-α (TNF-α) could be caused by free radicals, which could lead to gene expression and DNA oxidation. Additionally, free radicals could increase the production of reactive oxygen species (ROS) in addition to reactive nitrogen species (RNS). So, various cell types have shown A rise in pro-inflammatory cytokine expression and ROS generation in response to high glucose levels [5].

Peripheral neuropathy and vascular disease are the main causes of diabetic foot, resulting in in the ulceration of the foot. The progression of this ulceration, together with infection and/or soft tissue loss, can lead to difficulties walking and significantly impact one's quality of life [2]. Photobiomodulation therapy is a technique whereby low-level monochromatic, coherent light is applied to injured dermis in an attempt to improve wound healing. The non-thermal effects of photobiomodulation between 1–10 J/cm2 on biological tissues has been shown to be beneficial in cell culture studies [6].

Through photobiomodulation (PBM), various processes can be accelerated, including endothelial cell migration, proliferation, as well as organization for angiogenesis; infiltration by inflammatory cells for accelerated healing and immune surveillance; and wound contraction and increased fibroblast matrix production. To stimulate wound healing, PBM is utilized on many animal models, in vitro, as well as therapeutically with varying irradiances (power densities) and wavelengths. The problem is that the ideal combination of these factors has not been found [7].

Study design:

It was a single blinded randomized controlled trial study. The randomization was carried out utilizing computer-generated block randomization program.

Subjects:

Sixty-eight patients (males and females) with chronic neuropathic foot ulcer took-part in the study. Their ages ranged from fifty to seventy. They were selected from the

Author for Correspondence:

outpatient clinic at the Ismailia Medical Complex. The individuals were randomly assigned to one of two groups (n=34). Patients were allocated to 4 weeks. Assessment and measurements were done pre and post treatment.

Inclusion criteria:

All patients (males and females) were diagnosed as having neuropathic foot ulcer (two months after being diagnosed as diabetic). They were diagnosed as type II Diabetes Mellitus in chronic stage (controlled). Wound size was from 6-12cm2. Diabetic ulcers were classified as grade 2 and 3. This classification refers to partial thickness skin damage that affects the epidermis and/or dermis. The injury or necrosis of subcutaneous tissue could spread to but not via the underlying fascia, as well as superficial, abrasion, blister, along with the full thickness skin damage.

Exclusion criteria:

Present osteomyelitis, a life-threatening condition requiring intensive care [8]. People who had nerve damage or cellulites. Risk factors for immunosuppressive drug use include being pregnant, smoking, having a malignant condition, or getting cancer. We also ruled out venous and arterial disorders.

Every patient was distributed into two equivalent groups randomly:

Study group (A): Thirty-four Patients with chronic neuropathic foot ulcer were included in this group. The patients were treated with He-Ne LLL, which has a pulsed wave form, a visible ray, a wave length of 632.8 nm, and a peak potency of 30 mW, for chronic neuropathic foot ulcers. A dosage of 4 J/cm2 was administered. About twenty minutes elapsed throughout the session. In group B, patients received conventional treatment, which included three sessions of application per week for four weeks on the bottom of the foot, as well as regular sharp debridement of calluses that surround the ulcer, off-loading with walking or total-contact casts, along with regular moist dressing. Patients were told to apply only sodium chloride, a saline solution of 0.9%, for every-day asepsis of the ulcer [2].

Control group (B): Within this group were 34 patients, both men and women, who had a chronic neuropathic foot ulcer. Patients underwent traditional treatment, which included sharp debridement of ulcer-related calluses on a regular basis, off-loading with walking or total-contact casts, and moist dressing changes. They also received instructions to administer only sodium chloride, a saline solution containing 0.9%, for daily ulcer asepsis [9].

Each subject was asked to sign an informed consent form after having a thorough description of the study's protocol. Prior to the commencement of the study procedures, the Ethical Committee of the Faculty of Physical Therapy, Cairo University, Egypt, provided their approval to the protocol (No.P.T.REC/012/005238). The study was also registered with ClinicalTrails.gov with the ID (NCT06703762).

Instrumentations:

Evaluation instrument:

Recording data sheet:

All data as well as information of each participant in this study were included (name, age, address, affection of DM, history of affection, any history of foot trauma, any neuropathic symptoms).

Tools for evaluation:

Imito measure application: It was a smartphone application for measuring length, width, area and circumference by using a specialized marker for calibration and encircle the area of wound. Immediately after you take a photo, the app calculates the wound size. Imito wound measurement method is scientifically validated and replaces your wound ruler. Monitor the wound healing progress at one glance. [10].

Laboratory sample test: To measure the level of Interleukin 6 pre and post treatment for all patients in both groups [11].

Instruments for treatment:

Low level laser (He-Ne): It was used in the treatment of group A only.

Saline solution 0.9%: Concerning the daily asepsis of the ulcer) it was used for all patients in both groups [9].

Methods (Procedures):

Each participant in the trial completed an informed consent form after receiving a thorough description of the evaluation and treatment processes.

A- Evaluative procedures:

Length, width, area and circumference of the wound: it was measured by Imito measure application by using a specialized marker for calibration and encircle the area of wound. Immediately after you take a photo, the app calculates the wound size. Imito wound measurement method is scientifically validated and replaces your wound ruler. Monitor the wound healing progress at one glance.

Detection of Interleukin 6 level: It was identified by drawing blood samples from the cubital vein in every patient. A tube containing a pre-fabricated anticoagulant was used to transfer the collected blood samples. After 30 minutes of incubation in the tubes, the blood samples were transferred to a biochemical facility and centrifuged at 6,000 rpm for ten minutes. After removing the serum from the test tube, it was moved to the eppendorph tube. Interleukin 6 levels were measured after serum samples were kept at -80 ° C for analysis. Next, the serum Interleukin 6 level was determined [11].

B- Treatment procedures:

Low Level laser treatment: The LLLT with probe was administered to every patient in the study group. A red light with a wavelength of 632 nm was applied locally to the ulcer bed. Based on the size and depth of the ulcer, the period of exposure was determined to be 4J/cm2 for 20 minutes, with three sessions each week for four weeks of treatment. In order to expose the ulcer to the laser beam, each patient was instructed to lie down on their backs with the device probe, then the therapist asked the patient to wear the laser glass and not to look directly to the beam till the end of the session [12,13].

Conventional treatment: Dressings, antibiotics, blood pressure, cholesterol, along with diabetes control, aggressive pharmacological treatment, and wound debridement as necessary were all part of the standard care for diabetic wounds that all patients in both groups were given during, after, and prior to the laser therapy procedure.

Statistical analysis

The age comparison between the groups was done using an independent t-test. To compare the gender distribution among the groups, a chi-squared test was employed. The data was checked for normality using the Shapiro-Wilk test. In order to make sure that the groups were similar to one another, Levene's test for homogeneity of variances was performed. An independent t-test was used to compare the groups with respect to wound surface area and IL-6. We used a dependent t-test to compare the two groups both before and after the treatment. All statistical tests were required to meet a significance level of $p < 0.05$. An application developed by IBM SPSS in Chicago, IL, USA, known as SPSS, version 27 for Windows, was used for statistical analysis.

RESULTS

- Subject characteristics:

Groups A and B's subject characteristics are shown in Table (1). When comparing the groups according to gender and age, no statistically significant difference was found ($p > 0.05$).

Table (1): Comparison of subject characteristics among group A and B:

	Group A	Group B		
	Mean ± SD	Mean ± SD	t- value	p-value
Age (years)	59.56 ± 6.00	58.50 ± 6.56	0.69	0.49
Sex, N (%)				
Females	22 (65%)	21 (62%)	(χ^2 = 0.06)	0.80
Males	12 (35%)	13 38%)		

SD, Standard deviations; χ2, Chi squared value; p value, Probability value.

Table 2. Mean wound surface area and IL-6 pre and post treatment of group A and B:

	Group A	Group B			
	Mean ± SD	Mean ± SD	MD	t- value	p value
Wound surface area (cm²)					
Pre treatment	6.66 ± 1.68	6.62 ± 1.64	0.04	0.12	0.90
Post treatment	4.19 ± 1.27	6.06 ± 1.60	-1.87	-5.32	0.001
MD	2.47	0.56			
% of change	37.09	8.46			
t- value	18.97	16.69			
	p = 0.001	*p = 0.001*			
IL6 (pg/ml)					
Pre treatment	14.97 ± 4.83	14.81 ± 4.63	0.16	0.14	0.89
Post treatment	9.31 ± 2.46	11.89 ± 3.19			
MD	5.66	2.92			
% of change	37.81	19.72			
t- value	11.76	9.18			
	p = 0.001	*p = 0.001*			

SD, standard deviation; MD, mean difference; p-value, probability value

DISCUSSION:

For the impact of treatment wound surface area in both groups:

The findings indicated that both groups A and B's wound surface area significantly decreased after treatment compared to pre-treatment ($p = 0.001$), with group A's wound surface area significantly decreasing after treatment compared to group B's ($p = 0.001$).

Consistent with an earlier study by Saad and Desoky (2017) [14], the results showed that the ulcer size (both length and width) significantly improved in the group that was given LLLT in addition to conventional dressing following one week of therapy until 5 weeks, in compared with the control group that was given traditional dressing alone. The size of the ulcer decreased significantly during the course of treatment. One possible explanation is that infrared radiation therapy can enhance tissue oxygenation by increasing blood flow to ulcer tissue through improved microcirculation [15]. Also, it was in agreement with what Kajagar et al. (2012) found, which was that diabetic ulcers were much less after 15 days of infrared laser therapy interventions compared to a control group.

In addition, our findings corroborated those of an Iranian study by Kaviani et al. (2011) [17] that indicated foot diabetes lesions significantly diminished in size after the 4th week of LLLT treatment and healed entirely after twenty weeks. Furthermore, our findings were in line with those of Mathur et al. (2017) [18], who demonstrated that after two weeks of LLLT, the wounded area of 75% of patients with foot ulcers had reduced by 30-50% and more granulation tissue had formed. Researchers in Brazil found that diabetics' tissue regeneration rate of injuries improved significantly following LLLT treatment sessions [2].

However, our findings contradict those of Sobanko and Alster (2008) [19], who found no evidence that LLLT accelerates the healing process of human wounds. That's because it's difficult to compare clinical studies because of differences in laser parameters like wavelength, number of

treatment sessions, energy density, as well as where the ulcer started. For six weeks, they monitored LLLT over PU using infrared light at a dosage of 1 J/cm2 five times weekly, with wavelengths of 820 and 904 nm.

For the effect of treatment on Interleukin 6 area in both groups:

Both groups A and B had significantly reduced post-treatment levels of IL6 in comparison with pre-treatment levels ($p = 0.001$), with a statistically significant difference among groups A and B ($p = 0.001$).

These results came in agreement with those of Mrasori et al. (2021) [11], who found that after 6 weeks of conservative periodontal treatment using LLLT application in individuals suffering from Type 2 DM, the serum value of Interleukin 6 (TNF-α) was 11.26 ± 0.77 pg/mL, while following three months of therapy, it was significantly lesser than the values from the initial examination. The IL-6 values at 6 weeks (11.59 ± 0.71 pg / mL) and 3 months (11.41 ± 0.78 pg / mL) were not significantly different from the values at first examination (11.56 ± 0.81 pg / mL) in group B, which consisted of patients suffering from Type 2 DM who underwent conservative treatment without the use of LLLT. There was a significant difference in group A ($p<0.01$; $p= 0.001$) and group B ($p<0.01$; $p= 0.006$) at 3 months following treatment, according to the data, whereas both groups had corrected serum IL-6 concentrations favoring Group A.

On the other hand, our results came inconsistent with a study done by Ruh et al. (2018) [6] which was applied on an animal models their results showed no significant differences of Interleukin 6 levels after LLLT. We credit that to these previous study was applied on animal model so it's difficult to compare the results.

CONCLUSION

The result of the study concluded that adding LLLT in conservative treatment was very effective on wound healing and Interleukin 6 in patients with neuropathic foot ulcer. Overall, it would be preferable of adding photobiomodiolation in the form of LLLT to conservative treatment in the rehabilitation program of patients with peripheral neuropathies foot ulcer.

DISCLOSURE STATEMENT:

No author has any financial interest or received any financial benefit from this research.

CONFLICT OF INTEREST:

The authors stated no conflict of interest.

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