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Pulsed electromagnetic fields versus laser therapy on enhancing recovery of diabetic foot ulcer: A single blind randomized controlled trial.

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Abstract

Background: The nature of chronic diabetic foot ulceration disables the normal stages of healing, inducing a state of pathological inflammation resulting in a delayed healing process which predisposes the patients to infections. Purpose: This study was performed to compare between laser therapy and pulsed electromagnetic field (PEMF) therapy in management of infected diabetic foot ulcers. Design: A prospective, randomized, single-blind, pre–post-test, controlled trial. Setting: Participants were referred from the Outpatient Clinic Kasr El-Ani hospital to be treated in the Outpatient Clinic, Faculty of physical Therapy, Cairo University. The study was conducted between June 2015 and August 2016. Participants: Thirty participants with diabetic foot ulcers, their age ranged from 45-60 years. Interventions: The first group (GA) received 0.5 Gauss PEMF and the second group (GB) received 10 J/cm^2 Infra-red laser therapy. Main Outcome Measure: the primary outcome was wound surface area while the secondary outcome was colony count that were measured before the experiment and after 12 sessions of treatment. Results: Thirty participants with DFU (group A n=15; group B n=15) were randomized and analyzed. Comparing both groups post-program revealed that there was significant reduction in wound surface area in favor of (GB). However, no significant difference was found in colony count. Conclusion: 10 J/cm^2 infra-red laser and 0.5 Gauss. PEMF are two effective and recommended modalities in management of infected diabetic foot ulcer. However, laser therapy is better for wound regeneration regarding the same used parameters of treatment.

Keywords: Diabetic foot ulcers, PEMF, Laser, *Staphylococcus*.

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Introduction

The international diabetes federation has estimated number of people ranged from 20 to 79 years with diabetes 2015 in the Middle East and North Africa to be 35.4 million and growing to be 72.1 million by 2040. If this rise is not halted, by 2040 there will be 642 million people worldwide living with the disease [1]. Diabetes contributes to many multi-organ dysfunctions that include sensation affection, and lower limb amputation [1,2]. Diabetic foot ulcers (DFU) are defined as any skin breakdown on the foot of a diabetic person, including even minor irruption on the toes, heel, and the dorsal and planter foot [3]. A skin injury caused by a foot trauma or as a result of sensory or motor peripheral neuropathy is invaded by different microorganisms that proliferate and colonize the ulcer leading to tissue destruction, a host reaction and inflammation, manifested as clinical infection [4].

The nature of chronic diabetic foot ulceration disables the normal stages of healing, inducing a state of pathological inflammation resulting in a delayed healing process which predisposes the patients to infections [5]. It is believed that every 30 seconds a lower limb is lost somewhere in the world. For example; More than eighty thousand diabetic foot amputations in the United States is performed each year [3].

One in six diabetic foot ulcer patients will necessitate a limb amputation, bringing about a 5-year death rate of up to 77%, which is overcoming breast, colon, and prostate cancer and regardless of the progress in science and the multidisciplinary care systems, DFU treatment still a challenge to unsatisfactory results [2,6]. Laser therapy with its direct bio-simulative light

energy, is a new well known treatment modality stimulating wound healing process. The energy absorbed from the laser therapy has a negligible effect on tissue temperature yet stimulates cell molecules and atoms [7]. Laser therapy is a great promising tool of practice for the healing of chronic wounds and decreasing infection rate [8].

Pulsed Electromagnetic field (PEMF) is a non-invasive therapeutic technique exerts beneficial effects on wound healing. It's characterized by electromagnetic fields inducing micro-currents to a specific targeted tissue or the whole body. PEMF has been investigated as a therapy for wound healing and the results showed that PEMFs stimulate healing through increasing collagen synthesis, angiogenesis, and bacteriostasis [9]. Therefore, the purpose of this study was to compare between two well-known forms of electromagnetic radiations; PEMF and laser therapy in the form of photons, on infected DFU, as a serious common problem facing the diabetic population, regarding the wound surface area and bacterial colony count.

Subjects and Methods

Study design

The study was designed as a prospective, randomized, single-blind, pre–post-test, controlled trial. Ethical approval was obtained from the institutional review board at Faculty of physical therapy, Cairo University before study commencement. The study was followed the Guidelines of Declaration of Helsinki on the conduct of human research. The study was conducted between June 2015 and August 2016.

Participants

A convenient sample of thirty patients, 17 females, and 13 males, with diabetic foot ulcers (DFU) were recruited from the Outpatient Clinic Kasr El-Ani hospital to be treated in the Outpatient Clinic, Faculty of physical Therapy, Cairo University. They were enrolled and assessed for their eligibility to participate in the study. To be included in the study, patients had grade-2/Stage-D diabetic foot ulcers, according to University of Texas classification of diabetic foot, had a *Staphylococcus* bacterial infection, and their age ranged from 45-60 years. The participants were excluded if they were smokers, suffering from any autoimmune diseases, on immunosuppressive drugs, Concomitant psychiatric disorders, or contraindicated for the research adopted methods of treatment.

Randomization

Informed consent was obtained from each participant after explaining the nature, purpose, and benefits of the study, informing them of their right to refuse or withdraw at any time, and about the confidentiality of any obtained information. Anonymity was assured through coding of all data. Participants with DFU were randomly assigned into two groups (group A and group B) by a blinded and an independent research assistant who opened sealed envelopes that contained a computer generated randomization card. No subjects dropped out of the study after randomization.

Interventions

Participants were randomly assigned into group A (GA) received 0.5 Gauss (G) Pulsed Electromagnetic Field (PEMF) for 10 minute from supine lying position, in addition to the traditional medical treatment (Diabetic drugs only) and nursing care. The device (ASA model PMT Quattro PRO-Italy) was used in a frequency of 20 Hz. Group B (GB) received 10 J/cm² Infra-red laser therapy with 904 nm wavelength for 10 minute from supine lying position, in addition to the traditional medical treatment (Diabetic drugs only) and nursing care. The whole duration of each treatment session was calculated by the machine based on the energy density selected (10 J/cm²). Automatic scanning technique was adopted on both the wound bed and the wound perimeter intact skin. The device used is ASA model BRAVO Terza serie He-Ne Italy wavelength range of 632 nm to 904 nm. Both groups received 12 sessions of treatment, three times per week for four weeks.

Outcome measures

Wound surface area as the primary outcome was measured at the beginning and after one month of treatment; by tracing the wound perimeter using the transparency method in which the patient was positioned in a comfortable position with exposed foot, a sterilized transparent film was placed directly and in contact with the skin around the wound avoiding any movement or distortion of the foot. The wound margins were traced using a fine-tipped transparency marker three times for reliability. After tracing, the other side of the transparent film was cleaned with alcohol and the traced wound perimeters were transferred to an AutoCAD software program that measures the irregular shape areas in cm^2. As well as, Colony count as secondary outcome was measured before and after the whole duration of treatment (one month); A swab from the wound was taken from the wound by the same pathologist for all cases, placed in a sterile container, and sent to the laboratory. In the laboratory, that material was spread over the surface of several different types of culture plates and placed in an incubator at body temperature for one to two days. The number of colonies was counted. The bacterial load measurement was done by multiplying the number of colonies with dilution factor and the volume of the supernatant obtained during the tissue homogenization was presented as log CFU/ml [10].

Sample size and statistical analysis

To avoid a type II error, a preliminary power analysis (power (1-α error) P=0.85, α=0.05, effect size=0.92, with a two-tailed for a comparison of 2 independent groups) determined a sample size of 15 for each group in this study. This effect size was calculated according after a pilot study of 12 participants (6 in each group) considering the wound surface area as a primary outcome. Results were expressed as mean ± standard

deviation (SD). Comparison of different variables within and between groups was performed using paired and unpaired t test in normally distributed data or Wilcoxon Sign Rank test and Mann Whitney U test in not normally distributed data respectively. Statistical Package for Social Sciences (SPSS) computer program (version 22 windows) was used for data analysis. The alpha level was set at 0.05.

Table 1. *Descriptive statistics and unpaired t-tests for the mean age of the patients with diabetic foot ulcers for both groups; *Significant at the alpha level (p<0.05).*

Items	Group A		Group B		Comparison	
	Mean ± SD		Mean ± SD		t -value	P-value
Age (y)	55.13 ± 2.64		54.66 ± 3.59		0.405	0.689
	Females	Males	Females	Males	X^2-value	P-value
No.	11 (73.3%)	4 (26.7%)	6 (40%)	9 (60%)	3.394	0.065

Results

A total of 35 patients with DFU were eligible for inclusion, and 30 were randomized to study intervention. Group A (GA) consisted of 11 females and 4 males, while group B (GB) consisted of 6 females and 9 males, the mean age was 55.13 ± 2.64 and 54.66 ± 3.59 for GA and GB respectively. All randomized patients completed the trial. There were no statistically significant differences (P>0.05) between subjects in both groups concerning age. Also, Chi square revealed there were no significant differences between both groups in sex distribution (p>0.05) (Table 1) respectively.

For wound surface area; within groups: "Paired t test" revealed that there was a significant reduction of wound surface area (p<0.05) for both groups. Between groups: "unpaired t test" revealed that the mean values of the "pre" test between both groups (A and B) showed there was no significant differences (p>0.05). But, the mean values of the "post" test between both groups showed there was significant differences (p<0.05) and this significant reduction in favor of group B that received laser therapy.

For colony account; within groups: Wilcoxon Signed Rank tests" revealed that there was a significant decrease in the colony account in the "post" test (p<0.05) in compared with pretreatment at both groups. Between groups: "Mann-Whitney tests" revealed that the median score of the "pre" test between both groups revealed that there was no significant difference between the both groups (p>0.05).

As well as, the median score of the "post" test between both groups showed there was no significant difference between both groups (p>0.05) (Table 2).

Table 2. *Descriptive statistics of all dependent variables in patients with diabetic foot ulcers in pre and post treatment for both groups. *significant (p<0.05) difference between pre and post treatment; ¥significant (p<0.05) difference between groups at post treatment; IQR: Interquartile Range; SD: Standard Deviation.*

	Group A		Group B	
Measuring periods	pre	Post	pre	Post
Wound surface area (mean ± SD)	13.096 ± 5.93	5.84 ± 3.63*	17.55 ± 12.1	2.033 ± 2.01*¥
Colony account (median (IQR))	100000	1000*	100000	1000*

Discussion

The current study was performed to compare between two therapeutic modalities used in clinics to treat infected diabetic foot ulcers; the first is PEMF (0.5 G) compared to infra-red laser therapy 10 J/cm^2. Significant reduction in bacterial infection, wound surface area percentage of improvement has been proven for both modalities comparing pre-treatment to post-treatment. A significant difference in wound surface area percentage of improvement between the two groups has been found in favor of the laser group. In contrast to a non-significant difference in bacterial infection reduction between the two groups.

The importance of this study came from the facts that; diabetic foot is a common complication of diabetes easily prone to ulceration and consequently gets infected, and that both diabetes mellitus and infection affects the healing process making it very difficult for the wound to heal and a leading cause of amputation [11,12].

Diabetic foot ulcer is considered as a critical complication [13] especially after the appearance of drug resistance bacteria. Besides the lost resources of its management and its impact on the patient's life and productivity.

Another fact is that wound healing is a complex process contains many phases, mediators, and cell activities and that many modalities have been used and recommended in research to be used for such a medical problem and so, the complexity of the healing process, and the presence of various modalities, techniques and parameters, have made the selection criteria very confusing.

Despite the ambiguous underlying mechanism of PEMF, the interest in its use in wound healing has increased in the last two decades. PEMF is considered as a very promising modality that can be used clinically in wound control [13,14]. The results of

the current study proved that PEMFs have significantly accelerated wound closure and decreased infection in diabetic foot ulcers. These findings came in agreement with several studies that have proved the positive effect of PEMF on wound closure on both diabetic [11-13,15,16] and non-diabetic wounds [14-18]. However, other studies didn't support that, for example Milgram et al. [19], used high intensity magnetic field pulses and found there was no significant difference in terms of wound contraction, wound epithelialization, and contraction-epithelialization ratio between an experimental group received PEMF therapy and a sham group. Our study used 0.5 Gauss and 20 Hz. However, all the different results can be attributed to the used parameters and the different kind of wounds.

PEMF used to treat diabetic foot ulcers revealed the potentials to increase epithelial thickness [20], reduce inflammation and enhance cell proliferation and wound closure through its assured effect on capillaries in a study by [13], who found that PEMF increased capillary diameters and blood velocity in patients with chronic diabetic foot ulcers. This could be assured by the animal study of Guerriero et al. [14] that showed an increased response of fibroblast growth factor-2 (FGF-2), angiogenesis, and the induction of endothelial proliferation. Improved angiogenesis will enhance oxygen and nutrition at the wound area. Cheing et al. [16], proved that PEMF therapy has accelerated wound healing and myofibroblasts proliferation in induced diabetic rats' wounds. Myofiboblasts enhanced wound contraction and collagen deposition in diabetic wounds after exposure to PEMF therapy [11].

Cell dysfunction is the cause of most of the diseases, damaged cells have lower potential than normal cells, PEMF reestablish this difference [21], and may Augment the endogenous bioelectric current and alter some cellular activities such as DNA synthesis [14]. Our findings proved that there was a significant reduction in wound infection, colony count, post PEMF irradiation; other studies also mentioned the effect of PEMF inhibiting bacterial growth and production [14], decreasing *Staphylococcus aureus* colony-forming units [21], in addition to a histopathological inflammatory cells increase at wound area [20]. Impaired inflammatory phase of healing is a cause of delayed healing in chronic wounds. PEMF destroy bacteria releasing glycopolysacchrite that stimulate macrophages and body immunity [20].

This study also proved the effect of 10 J/cm^2 Infra-red laser therapy on healing of diabetic foot ulceration compared to the pre-treatment measures regarding wound surface area and the percentage of improvement. Some studies failed to prove the effectiveness of laser therapy on wound healing [22-25]. On the other hand, many more proved its effectiveness [2,7,26-30]. These might be attributed to the wide range of variables regarding phototherapy kind and parameters, technique of application, type of wounds, and the subjects, making it very difficult to conclude the exact cause any different findings. Nevertheless, the literature keeps reporting laser as treatment of a choice in wound care.

The exact mechanism of action for laser is not quietly fully revealed this is partly due to the complex nature of the wound healing process and also the lake of research evidence. However, the results of the current study can be explained based on the ability of laser to biostimulate the body cells, photobiomodulation, resulting in fibroblast proliferation and an increased number of fibroblasts [7], increased collagen fibers synthesis and concentration, as well as accelerated granulation tissue [27], greater wound contraction [28] plus neovascularization and early fast-growing epithelialization [7,29]. ATP synthesis and lymphocytic action is also increased [31] raising the whole cell level of energy and activity. Our study showed a significant bacterial reduction on the group treated with laser therapy compared to colony count pre-treatment. This might be due to the ability of laser therapy to recruit some important cytokines and growth factors such as interleukin-1 and interleukin-8 and its ability to stimulate phagocytosis of macrophages [2], eliminating bacteria which in turn accelerate the end of the inflammatory process and so accelerate the healing process through its bactericidal effect. However, this come in disagreement with another study [26] proved that 3 J/Cm^2 laser didn't have an effect on *Staphylococcus* infection *in vitro* study, the difference can be attributed to the used low energy intensity used and it is an *in vitro* study witch might affect the mode of application.

This study supports the use of both PEMF and laser therapies as an alternative and conjoint therapy with other antibiotics to manage wound infection. The two modalities are recommended in treatment DFU, they are applied from a distance with no risk of contact infection, they are painless and cheap compared to other surgical procedures that can be used for this kind of wounds regarding that 10 J/cm^2 Infra-red laser is better than 0.5 G and 20 Hz PEMF therapy. The study results are limited to the exact parameters used and sample selection. However, further studies should be conducted emphasizing on the underlying mechanism of action of PEMF and Laser, prolonged follow up, various modalities, parameters, and other kinds of wounds and population.

Conclusion

10 J/cm^2 infra-red laser and 0.5 G. PEMF are two effective and recommended modalities in management of infected diabetic foot ulcer. However, laser therapy is better for wound regeneration regarding the same used parameters of treatment.

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