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Additional effect of pulsed electromagnetic fields to laser therapy on management of diabetic foot ulcer: a single blind randomized controlled trial

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Diabetic Foot Ulcer (DFU) is a global health care problem considered as a major cause of morbidity and mortality among diabetic patients. Pulsed Electromagnetic field (PEMF) is a non-invasive technique with potential beneficial effects on wound healing. Laser therapy stimulates cell molecules and is strongly considered as a promising wound healing tool for chronic wounds. The aim of this study was to compare the effect of two therapeutic modalities used to treat infected DFU; the first is PEMF alone compared to PEMF added to infrared laser therapy in diabetic wound healing management. Methods: A prospective, single blind, controlled trial on thirty diabetic foot ulcer patients who were randomly assigned into group A (GA) receiving 2 Gauss (G) Pulsed Electromagnetic Field (PEMF) 10 minutes per session, in addition to the prescribed medical treatment (Diabetic drugs only) and nursing care. Group B (GB) received the same regimen of PEMF in addition to 5 J/cm² Infra-red laser therapy for 12 sessions. Statistical analysis showed that the adjuvant magnetic and laser therapy had more significant reduction in the colony count number in DFU ($P < 0.0001$). Infrared laser and PEMF are both effective and recommended modalities in reducing the infection of infected diabetic foot ulcer, however combining both modalities has better effect in managing diabetic foot wound infection.

Keywords: Diabetic foot ulcer, Laser, Pulsed Electromagnetic field

INTRODUCTION

Diabetes is an endocrine disorder that might affect many systems leading to various dysfunctions leading to poor sensation and possibly amputation (Tchanque-Fossuo et al., 2016). Diabetic foot ulcers (DFU) are defined as any breakdown the foot skin of a diabetic person. (Brem, Sheehan, Rosenberg, Schneider, & Boulton, 2006). DFU can be considered as a primary cause of morbidity and mortality affecting diabetic patients with a worldwide epidemiology. Recent reporting from WHO (WHO, 2011) estimates the number of diabetic patient as 347 million, with a proportion of 1 possible development of diabetic ulcer in each 20 patients. The Middle East and North Africa (MENA) represent highest prevalence of diabetes occurrence where Egypt is ranked among the top

10 countries(WB, 2013). The International Diabetes Federation (IDF) estimates that 7.5 million Egyptian adults are diabetics, and might reach 13.1 million by 2030(IDF, 2013). The number of diabetic patients is rising yearly at a rate greater than expected. It is estimated that the number of diabetic patients in Africa and the Middle East to be 35.4 million, with a possible increase to around 72.1 million by 2040 (Guariguata et al., 2014). Such rise in diabetes prevalence is also expected to be correlated with higher rate of occurrence of DFU and consequently possible secondary amputation (Ziegler-Graham, MacKenzie, Ephraim, Travison, & Brookmeyer, 2008).

The physiopathology of DFU make it liable to be invaded by colonizing microorganisms resulting in more tissue destruction with a cascade of inflammatory reactions (Lipsky et al., 2012) hindering the healing process (Nteleki & Houreld, 2012). DFU treatment is considered as a challenge with high prevalence of failures. Lower Limb amputation is the end result in the management process for one per six DFU patients with five year mortality competing with mortality rates correlated with many cancer such as breast, prostate, and colon (Beckmann, Meyer-Hamme, & Schröder, 2014). About 80,000 patients are subjected to foot amputations in the United States secondary to DFU. Worldwide, it is estimated that every 30 seconds a lower limb amputation is executed (Brem et al., 2006). When examining the rate of lower limb amputations from diabetes compared to other causes, DFU amputation exceeds 28 times amputations from other causes (Ziegler-Graham et al., 2008).

DFU management includes control of blood sugar level, patient education regarding foot care, compression, debridement, control of infection, limb elevation and revascularization surgeries. Lower limb amputation is usually a result of poor wound care (Ayello, 2005). It is considered that failure of wound healing through standard interventions in less than two weeks must urge a reevaluation and more robust and advanced interventions must be implemented. Such interventions are usually more costly and might include pulsed electromagnetic fields intervention and phototherapy (Mulder, Tenenhaus, & D'Souza, 2014).

Pulsed Electromagnetic field (PEMF) is a novel non-invasive technique used in wound healing through introducing micro currents of electromagnetic fields to the targeted tissues. PEMF has been claimed to enhance collagen synthesis, angiogenesis, and bacteriostasis consequently fostering wound healing (Shupak, Prato, & Thomas, 2003). PEMF may be beneficial in addressing wound healing among both diabetics and non-diabetics and can be useful also in ulcer prevention and hence reduction of amputation prevalence and thus requiring more scientific research to prove its effectiveness (Callaghan et al., 2008).

Another novel intervention in approaching DFU include laser light application through inducing energy at a specific wavelength. It has been claimed that such intervention might activate enzymes responsible for cell metabolism by means of minimal changes in temperature well known as phototherapy. This energy is also absorbed by chromophores thus increasing mitochondrial activity and finally rising ATP as well (Silveira et al., 2009). Laser therapy has been claimed to stimulate cell molecules and atoms(Feitosa et al., 2015), and is strongly advised as non-invasive tool to address wound healing in cases of chronic wounds(Tubachi & Godhi, 2015).

Hence, the aim of this study was to compare between two well-known forms of electromagnetic radiations; PEMF and laser therapy in the form of photons, on DFU among diabetic patients regarding the wound surface area and bacterial colony count.

MATERIALS AND METHODS

Study design

The study was a prospective, single blinded, pre–post-test, randomized controlled trial. Ethical approval was obtained from the institutional review board at Faculty of physical therapy, Cairo University before study commencement. The study followed the Guidelines of Declaration of Helsinki on the conduct of human research. The study was conducted between June 2017 and August 2017.

Participants

Thirty, Type II, diabetic patients suffering also from diabetic foot ulcers (DFU) were recruited from the Outpatient Clinic Kasr El-Aini hospital to be treated in the Outpatient Clinics, Faculty of Physical Therapy, Cairo University. Patients were assessed for their eligibility to participate in the study. The participants had grade-3/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, alcoholic, suffering from any autoimmune diseases, on immunosuppressive drugs, in addition to any concomitant psychiatric disorders, or contraindicated for the research-adopted methods of treatment.

Randomization

All patients underwent a session regarding their willingness to participate in the study. 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.

All data was coded to assure anonymity was assured. Participants with DFU were randomly and blindly assigned into two groups (group A and group B) by an independent research assistant who opened sealed envelopes containing a computer generated randomization card. No dropouts were recorded after randomization.

Interventions

Participants were randomly assigned into group A (GA) receiving 2 Gauss (G) Pulsed Electromagnetic Field (PEMF) 10 minutes per session in supine position, in addition to the prescribed medical treatment (Diabetic drugs only) and nursing care. The device used was (ASA model PMT Quattro PRO-Italy) at 20 Hz of frequency. Group B (GB) received the same dose of PEMF in addition to Infrared laser therapy with 904 nm wavelengths with a 5J/cm² density for 10 minute in supine position, in addition to the prescribed medical treatment (Diabetic drugs only) and nursing care. The whole duration of each treatment session was set by the machine based on the density selected (5J/cm²). Infrared laser therapy was applied using automatic scanning technique on both the wound and the wound perimeter intact skin. The device used was ASA model BRAVO Terzaserie 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 in order to measure the irregular shape areas in cm^2. Additionally, colony count, as secondary outcome, was measured before and after the whole duration of treatment (one month); using a sterile swab, the same pathologist collected specimen from the wound, placed it in a sterile container, and sent to the laboratory. In the laboratory, the specimen was spread over several different types of culture plates and placed in an incubator at 37°C 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 (Zhao et al., 2012).

Sample size and statistical analysis

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 23 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 in both groups.

Items	Group A	Group B	Comparison		Level of significance
	Mean ± SD	Mean ± SD	t-value	p-value	
Age (yrs)	55.13±2.64	56.46±3.22	1.238	0.226	NS

*SD: standard deviation, P: probability, S: significance, NS: non-significant.

Table (2): Distribution of sex in both groups:

	Group A		Group B		Chi -Square	
	Females	Males	Females	Males	X^2	p-value
No.	11 (73.3%)	4 (26.7%)	8 (53.3%)	7 (46.7%)	1.292	0.256
Total	15 (100%)		15 (100%)			

*Significant at the alpha level (p < 0.05).

Table (3): Median score, U, Z, and P values of the colony account pre and post treatment in both groups.

Colony account	Median score		Z-value	p- value
	pre	Post		
Group A	100000	1000	-3.305	0.001*
Group B	100000	100	-3.413	0.001*
U-value	112.5	22		
Z-value	0.000	-3.867		
p- value	1.00	0.0001*		

*Significant level is set at alpha level <0.05

RESULTS

Baseline and demographic data

There were no statistically significant differences (p>0.05) between subjects in both groups concerning age (Table 1).

In addition, Chi square revealed no significant differences between both groups in sex distribution (p>0.05) (Table 2).

Within groups:

The median score of colony account in the "pre" and "post" treatment were 100000 and 1000 respectively in the group A. Statistical analysis using the non-parametric Wilcoxon Signed Rank tests revealed that there was a significant decrease in the colony account in the "post" test in the group A (p <0.05). Meanwhile, the median score of colony account in the "pre" and "post" tests were 100000 and 100 respectively in the group B. statistical analysis using the non-parametric "Wilcoxon Signed Rank tests" revealed that there was a significant decrease in the colony account in the "post" test in the group B (p<0.05) table(3).

Between groups:

Considering the effect of the tested group (first independent variable) on colony account, "Mann-Whitney tests" revealed that the median score of the "pre" test between both groups revealed no significant difference between both groups (p>0.05). Additionally, the median score of the "post" test between both groups showed significant difference between the both groups (p<0.05) and this significant reduction was in favor to group B (Table 3).

DISCUSSION

The study was conducted to compare the effect of two therapeutic modalities used to treat infected DFU; the first is PEMF (2 G) alone compared to PEMF (2 G) combined with infra-red laser therapy at 5 J/cm^2. Patients in this study were 30 with type II diabetes mellitus and suffering from stage 3 DFU. Participants were distributed into two groups A&B. Group A where the patients were subjected to 2 Gauss, 10 minutes' sessions, of Pulsed Electromagnetic Field Therapy (PEMF) only, for 12 sessions every other day each. Group B were subjected to the same treatment regimen as group A in addition to 5 J/cm^2 of Laser therapy during each treatment session. The patients in the two groups were homogenous regarding age and sex with no significant differences (p= 0.226) and sex (p= 0.256).

PEMF alone showed remarkable effect in reducing DFU colony count with significant differences after therapy from 100000 to 1000 (p<0.0001). More marked reduction in the colony count was found in the intervention group B receiving a combination of both PEMF and Laser therapy from 100000 to 100 with evident statistical significance (p<0.0001). Statistical analysis showed that the combined effect of magnetic and laser therapy had more significant reduction in the colony count number (p<0.0001). Diabetic foot is

a common complication of diabetes and is usually robust towards healing and it is easily subjected to infection, both infection and diabetes are main reasons for non-healing or delayed healing sometimes leading to amputation as an end result to prevent the spread of infection (Guerriero et al., 2015). When considering drug resistance bacteria, DFU is considered as a challenging critical complication affecting patient's productivity and normal life. Wound healing is a complex process requiring several cell activities, mediators over different healing phases; research potential in this field is highly recommended. Comparing the results of the current study with others is somehow confusing due to the differences in study designs, selection criteria, healing process complexity, differences in the parameters and techniques and the presence of various treatment modalities.

Despite the lack of consensus on the underlying mechanism of action of PEMF, it is postulated to be a promising wound healing modality (El Rasheed, Mahmoud, Hamada, & El Khatib, 2017).The current study proved that the use of PEMFs alone have significantly decreased infection and colony count after irradiation in DFUs. These findings came in agreement with several studies that have proved the positive effect of PEMF on DFU healing (Cheing, Li, Huang, Kwan, & Cheung, 2014; Choi, Cheung, Li, & Cheing, 2016; Guerriero et al., 2015). Other studies reported also the inhibitory effect of PEMF on bacterial growth and production(El Rasheed et al., 2017), *Staphylococcus aureus* colony-form reduction(Ahmed, Istivan, Cosic, & Pirogova, 2013)and destroying the glycopolysaccharide releasing bacteria that stimulate macrophages and hence body immunity(Ibrahim, Nazal, & Alrashid, 2011).On the other side Milgram et al(Milgram, Shahar, Levin-Harrus, & Kass, 2004) who used high intensity PEMF reported no significant differences in terms of wound contraction and epithelialization. Our study used 2 Gauss of FEMF differences in results may be attributed to the differences in the kind of wounds and the used parameters.

Previous studies proved the Infra-red laser therapy ability to enhance the healing process of the wound via its bactericidal effect through recruiting important growth factors and cytokines as interleukin-1 and interleukin-8 and stimulating phagocytic effect of macrophages (Tchanque-Fossuo et al., 2016).This was proved by significant bacterial reduction on the group treated with Infra-red laser therapy at 10 J/cm² compared to colony count pretreatment and thus improved DFU healing process(Choi et al., 2016)[21].Many studies have proved the effectiveness of laser therapy on wound healing (Feitosa et al., 2015; Pereira, De Paula, Cielinski, Pilonetto, & Von Bahten, 2014; Tchanque-Fossuo et al., 2016). Minatel et al (Minatel, Frade, França, & Enwemeka, 2009) reported that Laser irradiation promoted DFU healing which resisted formerly to other forms of treatment. On the other hand, some studies failed to prove that (Lagan, Clements, McDonough, & Baxter, 2001). The type of wounds, technique of laser therapy application, difference in the recruited subjects and the phototherapy parameters ranges could be the attributing factors beyond the lack of universal agreement on laser as a treatment choice of wound healing.

Other researchers (El Rasheed et al., 2017) supported the use of combined PEMF and laser as alternative therapies with antibiotics to manage wound infection deducing that 10 J/cm2 Infra-red laser is better than 0.5 G and 20 Hz PEMF therapy. The two modalities are applied safely from a distance creating no risk of contact infection, painless and cheap when compared to surgical interventions making them highly recommended in treatment DFU. The current study results supported that the combination of PEMS 2 Gauss and laser therapy5 J/cm² had more significant reduction in the colony count number ($p < 0.0001$).

The study results are limited to the selected sample with the exact parameters used. Further studies should be encouraged to find out the underlying mechanism of action of PEMF and Laser. Long-term follow-up, application of different treatment modalities, measurement of various parameters, and inclusion of other kinds of wounds and population is recommended in further researches.

CONCLUSION

The combination of 5 J/cm2 infra-red laser and 2 G. PEMF are effective and recommended modalities in reducing the infection of infected diabetic foot ulcer. Combining both modalities has shown more remarkable reduction in wound infection regarding the same used parameters of treatment.

CONFLICT OF INTEREST

Authors declare no potential conflicts of interests.

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AUTHOR CONTRIBUTIONS

NAE, HAH, AMA, GSS, and RB proposed the research idea and design, NAE, HAH, AMA, performed the practical part, and helped in writing the manuscript. HAH, AMA, GSS, and RB designed the experiment, performed the statistics, writing and reviewing the manuscript. All authors read and approved the final version.

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