Research Article

Interleukin-6 response to shock wave therapy versus polarized light therapy in the treatment of chronic diabetic foot ulcers

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ABSTRACT

Background: Diabetic foot is one of the most feared complications of diabetes mellitus (DM) characterized by definite inflammatory reaction as one of the DM complications. Foot ulcers are one of the danger complications among diabetic patients. The ulcers can be inflamed after the period of time and lead to pain and disability. The advancement of foot ulcer can cause amputation of lower limb. **Purpose:** The aim of this study was to investigate the response of interleukin 6 (IL-6) and ulcer surface area to shock wave therapy versus polarized light therapy in chronic diabetic foot ulcer. **Materials and Methods:** A total of 45 diabetic patients with chronic foot ulcer participated in the study, their age ranges from 55 to 65 years of age. They randomly assigned into three groups, Group A (15 patients) received shock wave and traditional wound care, Group B (15 patients) received polarized light therapy and traditional wound care, and Group C (controlled group) (15 patients) received traditional wound care only. Subjects were assessed pre and post 2 months of study. The foot ulcer is measured by planimeter method and IL-6 was measured by enzyme-linked immunosorbent assay. **Results:** The shock wave and polarized light therapy groups show significant improvement of foot ulcer surface area and lowering of IL-6 ($P < 0.05$) but not significant in controlled group ($P < 0.05$). **Conclusion:** Both polarized light therapy and shock wave therapy are effective in increasing the healing of diabetic foot ulcer and lowering of IL-6, but polarized light therapy is more effective than shock wave therapy in increasing the healing of diabetic foot ulcer and lowering of IL-6.

KEY WORDS: Interleukin 6, Polarized light therapy, Shock wave

INTRODUCTION

Diabetes mellitus (DM) is a complex metabolic disorder characterized by hyperglycemia, which results from either an absolute deficiency of insulin (Type 1 DM) or insulin resistance with or without abnormal insulin secretion (Type 2 DM [T2DM]). Approximately 90–95% of individuals with diabetes suffer from T2DM.[1]

The most common complication of diabetes is peripheral arterial disease and neuropathy, the patient complains of loss of sensation due to neuropathy and coldness in peripheral extremity due to ischemia. The combination of them will lead to foot ulcer.[2]

The amputation is highly found in diabetic patient due to infection disease and increase risk of death[3] foot ulcers occurred about 15% of patient with diabetes throughout their life with occurrence of 1–4%.[4]

Altered blood circulation, ulcers, and amputations are the most common complication of diabetes. Diabetic foot ulcers lead to increased level of morbidity, disabled persons, cost of treatment, and high level of amputations. Most of lower extremity amputations are due to diabetes.[5]

Many different factors will lead to diabetic foot ulcer, such as foot deformity, peripheral neuropathy, visual impairment, and arterial peripheral disease; all of these factors occur with high recurrence and severity in diabetic patient.[6]

Pro- and anti-inflammatory mediators are important in the different phases of wound healing, as any changes in immune system can interfere with tissue homeostasis and delay wound healing. After the appearance of ulcers and persist for long time that can

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lead to chronic, non-healing ulcers which is known by diabetic foot syndrome.[7]

A chronic state of low-level inflammation is related with the pathogenesis of T2DM. This low-level inflammation represents itself, among other things, by elevated circulating levels of inflammatory cytokines such as interleukin 6 (IL-6).[8]

T-cells and macrophages secrete IL-6 which is a multifunctional cytokine in case of infection and inflammation to stimulate immune reaction. Indeed, this cytokine is involved in the inflammatory response associated with insulin-resistant state.[9]

IL-6 is multifunction cytokine with 183 amino acids. It has a major role in acute-phase response, bone metabolism, growth of tumor cells, and inflammation. IL-6 is a primary cause of fever, acute-phase reaction which occurs in liver, and changes from acute to chronic inflammatory disease. It takes part in many inflammatory cases such as inflammatory bowel disease and arthritis.[10]

Shock wave has been appeared to advance the formation and improvement of blood vessels (angiogenesis) and to decrease inflammation.[11] Many studies on animal models have approved that there is an elevation in levels of proteins such as vascular endothelial growth factor (VEGF) and factor hypoxia-inducible factor 1-alpha after treatment. These proteins take a part for the regain of tissue oxygen supply when blood flow is insufficient.[12,13] This angiogenic process is occurred after shock wave treatment and assumed a significant role in healing wound.[14]

Polarized light therapy is a relatively new therapeutic intervention. In this procedure, a polarized linear and polychromatic light was used. The wave of light travels in parallel planes creating a thin and focused beam. In contrast the common light, where its waves moves through a space in all directions, polarized light originates from refraction of basic light through special covered mirrors to be gone through photograph filter channels.[15]

Polarized light had a great impact for the improvement of the cell membrane functions, elevating the production of adenosine triphosphate in mitochondria. Besides, it diminished the inflammation and increased microcirculation, tissue oxygenation, proliferation of fibroblast, formation of collagen, and enhancement of epithelialization. Due to improving these functions, this method was promising to accelerate wound healing.[16] Therefore, the aim of this study was to measure the IL-6 concentration in chronic diabetic patient with foot ulcer after treatment by shock wave therapy and polarized light therapy and compare the result to show the effectiveness of each one.

MATERIALS AND METHODS

Trial Design

This is a single-blind, parallel-group, active-control, randomized controlled trial, 45 diabetic patients from both sexes (22 females and 23 males) with Grade IIade es) with(according to University of Texas classification)[17] with duration ranged from 1 to 2 months participated in this study. An informed written consent was obtained from each participant.

Participant

The practical work was done from April 2019 to June 2019. The patient was referred to physical therapy outpatient clinic, Faculty of Physical Therapy, Deraya University, from vascular and general surgery outclinics in Faculty of Medicine, Minia University Hospital. Their ages ranged between 55 and 65 years. Patients were randomly classified into three groups of equal numbers by one-to-one way: Group A (15 patients) received shock wave and traditional wound care, Group B (15 patients) received polarized light therapy and traditional wound care, and Group C controlled group (15 patients) received traditional wound care only, all patients in the three groups received the same medical treatment.

The inclusive criteria

Diabetic patients with foot ulcer, their age ranged from 55 to 65 years, the period of ulcer development is 2 months at least, the foot ulcer is Grade 2, and surface area wide is more than 1 cm^2.

Exclusive criteria

Patients with renal failure, pregnant, malignancies, undertreatment of radiotherapy or chemotherapy, anemia, hyperthyroidism, alcoholic addiction, the surface area of ulcer is more than 10 cm^2, and Grade 4 (Stage IV, loss of full thickness of soft tissue and reach deep into muscle, bone, tendon, and joint capsule) were excluded from the study.

Evaluation and treatment procedures were accomplished in the physical therapy outclinic, Faculty of Physical Therapy, Deraya University.

Randomization

The patients were randomly assigned into three groups equal in number (the experimental A, B group and the control group C) using block randomization.

Intervention

Group A (shock wave group)

This group was treated with shock wave plus traditional wound care and medical treatment. At the beginning, the ulcer should be clean, the head of shock wave device was directed over the ulcer; the

cleaned ulcer was secured with clean ultrasound gel and a clean wrap. The head was then moved directly on the ulcer and its edge. The frequency of treatment was a session every 1 week, with 500 pulses per 1 cm^2 delivered in ulcer at every session with 0.1 mJ/mm^2 density.[18]

The ulcer was dressed after treatment session, the patient reported about any symptoms during session or any side effect after the treatment, the duration of session was 3 min, the protocol consisted of eight sessions, one session every week for consecutive 8 weeks, the patient was followed up every week to check the prognosis of ulcer. The probe was cleaned with alcohol to keep away from any infection.

Group B (polarized light therapy group)

Bioptron Pro 1 Class II (Switzerland) device, the wavelength of polarized light ranged from 480 nm to 3400 nm. The head of the device was vertically applied on the ulcer area. The distance of device and ulcer was 10 cm. The level of polarization was >95%. The power density was 40 mW/cm^2. It is equal to an energy density of an average of 2.4 J/cm^2 per minute.[19]

The time of session was 8 min. The frequency of treatment was 3 times per weekday after day for consecutive 8 weeks.

Group C (controlled group)

The patients in this group were treated by traditional wound care, specifically debridement, sufficient pressure relief, and treatment of infection according to international rules.

Outcome Measures

A thorough medical history was taken from each patient before enrollment; the following evaluative procedure was done before and after the intervention.

The planimeter method was used in this study to measure ulcer surface area, the piece of sterilized transparency film was placed over the ulcer and following by fine-tipped transparency marker. The traced transparency film sets over carbon paper, there is a white paper which was placed between them, the traced film was converted into metric graph paper and calculated the numbers of square millimeters on the graph paper within the ulcer surface area (only full 1 mm^2 inside the perimeter was counted) and the area was converted to square centimeters. The measurement reliability was established by repetition of tracing process 3 times. The ulcer surface area was measured by average mean of successive three trails.[20] This measurement was done before and after treatment which lasts for 8 weeks.

Enzyme-linked Immunosorbent Assay (ELISA)

Blood sample test was drawn from every patient in the study groups. Immunomicrobiologic examination was done to estimate the level of different IL-6 by ELISA.

Data Analysis Sample Size Calculation

The current test involved two independent variables. The first test was the tested group; between-subject factors which had three levels (Group A, Group B, and Group C). The measuring periods were the second test; within-subject factor which had two levels (pre-treatment and post-treatment). In addition, this test involved three tested dependent variables (IL-6 and USA). Before final analysis, information was screened for normality assumption, similarity of variance, and appearance of extreme scores. This investigation was done as a prerequisite for parametric calculations of the analysis of difference. IL-6 and USA were normally distributed, as assessed by Shapiro–Wilks test ($P > 0.05$). There was homogeneity of variances, as assessed by Levene's ($P > 0.05$) for all variables. There was a linear relationship between the dependent variables, as assessed by scatterplot, and no evidence of multicollinearity, as assessed by Pearson correlation ($|r| < 0.9$). There were no univariate outliers in the data, as assessed by inspection of a boxplot, and no multivariate outliers in the data, as assessed by Mahalanobis distance. Accordingly, 3 × 2 mixed multivariate analysis of variance (MANOVA) test was used to compare the tested variables of interest at different measuring periods at three groups. The alpha level was set at 0.05.

RESULTS

The one-way ANOVA test revealed that there were no significant differences ($P > 0.05$) in the mean values of age, body mass, height, and body mass index among three tested groups [Table 1].

Statistical analysis using mixed design MANOVA revealed that there was significant within-subject effect (F = 320.496, $P = 0.0001$) and treatment × time effect (F = 41.326, $P = 0.0001$*), while there

Table 1: General characteristics of subjects in the study groups

General characteristics	Group A	Group B	Group C	F	*P*
Age (years)	59.47±3.292	60.73±2.789	58.27±3.105	1.3488	0.27055
Body mass (kg)	72.93±6.85	74.4±5.501	75.87±5.502	0.6287	0.53818
Height (cm)	175.67±7.394	175.47±6.3	173.4±4.657	0.9009	0.41390
Body mass index (kg/m^2)	23.97±1.309	24.14±0.783	24.16±1.629	1.6866	0.19744

Table 2: Descriptive statistics and multiple pairwise comparison tests (*post-hoc* tests) for all dependent variables for three groups at different measuring periods

Variables	Group A		Group B		Group C	
	Pre	Post	Pre	Post	Pre	Post
IL6	184.46±35.11	62.26±15.08	180.26±34.04	33.06±17.36	177.86±35.34	177.73±35.53
USA	7.17±1.5	2.67±0.56	7.3±1.9	1.54±0.98	7.04±1.83	7.02±1.76
Group	**Within groups (pre vs. post) *P*-value**					
	IL-6			**USA**		
Group A	0.0001*			0.0001*		
Group B	0.0001*			0.0001*		
Group C	0.984			0.97		
Group comparison	**Among groups**					
	IL-6			**USA**		
	Pre-treatment	**Post-treatment**		**Pre-treatment**	**Post-treatment**	
Group A versus B	0.999	0.006*		0.999	0.044*	
Group A versus C	0.999	0.0001*		0.999	0.0001*	
Group B versus C	0.999	0.0001*		0.999	0.0001*	

*Significant at the alpha level (P<0.05). IL-6: Interleukin-6

was significant between-subject effects (F = 19.109, P = 0.0001*). Table 2 presents descriptive statistics (mean ± standard deviation) and multiple pairwise comparison tests (*post hoc* tests) for all dependent variables. In the same context regarding within-subject effect, the multiple pairwise comparison tests revealed that there was a significant reduction (P < 0.05) in IL-6 and USA at Group A and Group B, while there was no significant difference (P > 0.05) at Group C in the post-treatment condition compared with the pre-treatment. Regarding between-subject effects, multiple pairwise comparisons revealed that there was a significant reduction (P < 0.05) in IL-6 and USA (P < 0.05) in favor to Group B in compared to Group A and C. As well as, while there was a significant reduction in favor to Group A in compared to Group C.

DISCUSSION

The shock wave has been appeared to improve blood supply, increase cell proliferation, and initiate neovascularization by stimulation of VEGF and endothelial nitric oxide synthase and reproduction of cell nuclear antigen.[21] The ischemic area is reduced after the treatment of shock wave by increasing tissue perfusion and reduction of the inflammatory response.[22] Many mediators released after the application of shock wave such as growth factor beta-1 and insulin-like growth factor-1 that prompting recruitment of skin fibroblasts, lowering of inflammatory response, and increasing of wound healing mostly the chronic ulcers.[23]

In the study, after the treatment of extracorporeal shock wave therapy on 32 patients with chronic ulcer, there is completely recover of 16 patients after six sessions and the rest of patients there is decrease in ulcer size, but the study did not mention the changes between groups in ulcer size.[24]

The shock wave is safe intervention on patients with ulcers, as this approved by a study done on 208 patients with different type of ulcers, as there are 31 patients with neurovascular cause of ulcer, after the treatment of shock wave, there is a significant improvement in ulcer size and no side effect.[25]

The polarized light which is emitted by Bioptron device has many characters as; the waves of polarized light oscillate on parallel planes, incorporate a wide transmission capacity. The range of its wavelength is 480 nm–3400 nm, incoherent light, low-energy density that reaching the skin with a constant intensity. This density has biostimulative impacts.[26]

These results come in agreement with Colić *et al*., 2004, researched the impact of polarized light treatment on 462 patients who had facial reconstruction surgery, each patient got Bioptron treatment to the other sides of the face just and the opposite side served as the control, the face group: 26 (57.8%) significant and 11 (24.4%) no difference; blepharoplasty group: 48 (71.6%) significant and 6 (8.9%) no difference; and facial ancillary group: 164 (46.9%) significant and 127 (36.3%) no difference.[27]

There is a study on 52 cardiac carcinoma patients with the left thoracophrenolaparotomy wound. The study is standard care for one group and other groups delivered Bioptron light therapy plus standard care daily for 10 days starting on the 2nd day of operation, the distance of Bioptron device from skin surface is 15 cm, outcomes were significantly better in the Bioptron group on the 12th post-operative day.[28]

A total of 45 elderly patients with venous ulcers, they randomized into three groups, one received electroionizing treatment, other Bioptron light therapy and controlled

group standard care only, and ulcers were cured more in experimental groups than the control group. Light therapy group demonstrated slightly better overall results when scores for all parameters of ulcer healing were totaled.[29]

CONCLUSION

The finding of this study revealed a significant reduction of IL-6 after treatment by shock wave and polarized light therapy at the end of this study and showed improvement in cure diabetic foot ulcer. Both shock wave and polarized light therapy can be viewed as a useful treatment of wound healing. They can accelerate wound healing through the stimulation of regenerative processes and anti-inflammatory effect. Finally, polarized light therapy is progressively successful in accelerating the healing of diabetic foot ulcer and reduction of IL-6 level than shock wave therapy.

DISCLOSURE

The authors do not have any commercial concerns regarding this article.

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