Key words: Pulsed High Intensity Laser, Wound Healing, Diabetic Foot Ulcer.

Effect of pulsed high intensity Nd:YAG laser in treatment of chronic diabetic foot ulcer.

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ABSTRACT

Delayed wound healing specially in diabetic ulcer is continuing challenge in rehabilitation medicine despite some recent advances in understanding of its basic principles and problems in wound healing that continue to cause significant morbidity and mortality. The aim of this study was to determine the effect of Pulsed High Intensity Nd:YAG Laser in the treatment of chronic diabetic foot ulcer (Deep Ulcer grade 2) and suggest laser protocol for wound healing. Forty patients suffering for chronic diabetic foot ulcer as a complication of diabetes mellitus, aged 40-70 years (mean age 58.17±9.83), were included. Patients were randomized for treatment in two groups. In the group A (HILT group), twenty patients received 24 session of pulsed high intensity Nd:YAG laser according to designed protocol, 3 times per week in addition to standard medical treatment which is given for diabetic foot patients. In the group B (Standard Medical Therapy Group), twenty patients received standard medical treatment for 24 sessions, three times per week. The result of this study revealed that there was statistical significant reduction in wound surface area for group (A) after 12 and 24 sessions. The results have demonstrated the objective effect of pulsed high intensity Nd:YAG laser in treatment of chronic diabetic foot ulcer. Therefore, pulsed high intensity Nd:YAG laser is effective, innovative, non invasive, non expensive and can be used as a new trend physical therapy modality in the treatment of chronic diabetic foot ulcer.

INTRODUCTION

Diabetes mellitus is the most common serious chronic disease which is characterized by hyperglycemia, metabolic abnormalities and long term complications involving eyes, skin, nerves and blood vessels. More than 220 million people had diabetes by the year 2010 and the majorities have type II diabetes [1].

Wound healing and tissue repair are complex processes that involve a dynamic series of events including clotting, inflammation, granulation tissue formation, epithelization, collagen synthesis and tissue remodeling [2].

Diabetic foot ulcer and subsequent foot amputation continue to cause considerable morbidity among persons with diabetes. Foot ulcer had been recognized as an important antecedent of lower extremity amputation in multiple studies. Progress has occurred in understanding the pathogenesis of these complications [3].

In recent years low intensity laser photostimulation has gained considerable recognition and importance among treatment modalities for various medical problems including wound repair processes, musculo-skeletal complications and pain control [4]. Also, laser is a new therapeutic tool used to reduce pain and to accelerate healing process of wounds [5].

Therapeutic lasers use monochromatic light in the 630 to 905 nm range, known as the "therapeutic window" [6]. High Intensity Laser Therapy (HILT), performed with a pulsed Nd:YAG laser, is characterized by a wavelength of 1064 nm that allows it to penetrate and spread more easily through the tissue due to not having endogenous chromophores able to efficiently absorb 1064 nm radiation. Moreover, with Nd:YAG pulses it is possible to deliver power peaks of up to 1000 Watt for times of 200μ seconds: extremely elevated peak intensity W/cm^2 in very brief times. Such a high intensity in such a short time prevents the heat accumulation by the tissues as happens with the use of Nd:YAG laser with continuous emission. These features result in a greater propagation of the radiation in the tissues with a very low histolesive risk, leading to the possibility of treating deep tissues and structures.

At the same time, the photothermal effect can be controlled in terms of patient safety and comfort by modulating pulse intensity and frequency [7].

Photostimulation promotes tissue repair by accelerating the production of collagen and promote overall connective tissue

stability in wound healing [2].
Powell et al [8] mentioned that fifteen percent or more of people with diabetes sustain one or more foot wounds during their life time and they are fifteen times more likely to suffer from non traumatic lower extremity amputation than people without diabetes. In addition, Margolis et al [9] revealed that diabetic patients with lower extremity ulcers were hospitalized longer on average than those who were hospitalized and did not have ulcers. Whereas half of all lower extremity amputations in hospitalized patients occurred in diabetic patients. They also assured that those with lower extremity amputation have a diminished quality of life, increased health costs, and more likely to have the contra lateral limb amputation, and are more likely to die within the next five years than those with no amputation.

The ulcer healing and its effects on the elongation of hospitalization period are major economical problems that face the physical therapists and other team members of ulcer rehabilitation. The importance of this study arises from the severity of diabetic foot ulcer which leads to serious complications such as: delayed wound healing, amputation and risk of infection. Diabetic foot ulcer problem may impair the primarily daily living activities due to the reduction of muscle power and the limitation of range of motion of peripheral extremities. Therefore, this study was designed to evaluate the effect of pulsed high intensity Nd:YAG laser in treatment of diabetic foot ulcer as a new physical therapy method for promoting healing process of chronic diabetic foot ulcer and to suggest a treatment protocol for wound healing by using pulsed high intensity laser.

MATERIALS AND METHODS:

Forty patients with chronic diabetic foot ulcer participated in this study. The patients suffering for unilateral or bilateral grade 2 deep ulcer diabetic foot ulcers (according to Wagner [10] Ulcer Classification System) lasting longer than two months were recruited in the study. The recruitment occurred via collaboration with general surgeons and wound care specialists serving outpatients clinics. All patients were selected from diabetic foot clinic in Alnour Hospital. All participants were informed about the nature and the purpose of the study; patients were examined by physician before the study to determine inclusive and exclusive criteria. Demographic information was obtained from standardized interview including age, sex, occupation, residence and special habits. Physical examination and history evaluation were conducted for all patients included weight, height, diabetes duration, ulcer duration and site, inspection of foot and palpation of peripheral pulses (anterior tibial artery and dorsalis pedis). Patient received an Arabic instruction manual that contains general advices about foot hygiene; nail care and foot wear to avoid future injuries. Patients were asked to do regular analysis of serum blood glucose level to maintain it within normal ranges during the program.
Subjects Criteria: Inclusive Criteria: patients with type II diabetes mellitus and grade 2 (Deep Ulcer) diabetic foot ulcers were referred from diabetic foot clinic in Alnour Hospital. Patient's age ranged from 40 to 70 years (mean age 58.17±9.83). All patients were male, and they did not receive any prior physical treatment for diabetic foot ulcer management. Exclusive Criteria: Patients had any pathological conditions or associated injuries which may affect the result of the study, patients had skin disease or any disease which leads to ulcer other than diabetes as venous or arterial ulcers, patients with malignancy, patients had any type of osteomyelitis associated with diabetic foot ulcer.
The patients randomly divided into two groups. Group A (HILT Group): twenty patients received application of pulsed high intensity Nd:YAG Laser (HIRO 3.0, ASA srl, Italy) for 24 sessions (about 8 weeks), three days per week in addition to standard medical treatment which is given for diabetic foot patients. Laser application was supplied immediately after standard medical treatment. HILT was given by 5 mm probe and energy densities 4 J/cm^2 with 1 cm distance from ulcer surface (non-contact), according to protocol designed for wound healing (Table 1). Group B (Standard Medical Therapy Group): twenty patients received standard medical treatment for 24 sessions. They were instructed to receive the treatment three times per week in the Physical Therapy Department; they received routine treatment of foot ulcer in form of hypoglycemic medications such as insulin injection to control blood glucose level, systemic antibiotics against microorganisms according to culture tests, debridement for removal of necrotic tissues and foreign bodies when needed, irrigation of the wound by normal saline solution twice daily, dressings after irrigation of the ulcer, and finally it was covered with sterile gauze.

Grade-0	High risk foot and no ulceration.
Grade -1	Superficial Ulcer.
Grade -2	Deep Ulcer (cellulitis)
Grade -3	Osteomyelitis with Ulceration or abscess.
Grade -4	Gangrenous Patches. Partial foot gangrene.
Grade -5	Gangrene of entire foot.

Tab. I. Wagner's classification for diabetic foot disease (Adopted from Levin and O'Neals).

Wound surface area (WSA) was measured by tracing the wound perimeter as reported by Kloth and Feedar [11] and by using a digital camera.
In the transparent method the patient was positioned in a comfortable position with exposure of the affected foot, double sterilized transparent plastic films were placed directly flat and attached to the skin around the wound area with avoiding any movement and distortion of the foot. Ulcer margins were traced by the same investigator to establish

reliability of measurements [12]. The ulcer perimeter was traced by using the film-tipped transparency marker. Each ulcer was traced three times to establish measurement reliability. After tracing, the side of the transparency film facing the ulcer was cleaned with a piece of cotton and alcohol. Carbon paper was placed over the 1-mm-squared metric graph paper. The traced transparency film was placed over the carbon paper with white paper in between and the tracing was transcribed onto the metric graph paper. WSA was calculated by counting the number of square millimeters on the metric graph within the wound tracing. The mean value of the three trials was calculated and taken to be the WSA. WSA measurements were taken at zero time ("pre"), after 12 sessions ("post -1"), and after 24 sessions ("post-2"), and after two weeks of follow up.

The digital camera was placed through a constant distance on a tripod from patient's foot to capture a colored picture of ulcer to detect the size changes of the ulcer before treatment and through 12 and 24 sessions of treatment. The environmental conditions such as patient position, camera distance and orientation and lighting level were controlled.

A 10 cm ruler was included in each photograph field to allow calibration during subsequent measurement procedures.

Designed protocol for laser applications (Table 1):

After calculating the area of the wound (Wound Surface Area (WSA) expressed in (cm^2), the dose applied for each wound was 4 J/cm^2 in each phase of laser treatment with a 10 minute total duration for all phases.

For example, for WSA=20 cm^2 the dose in each phase is 80 Joules.

RESULTS

Statistical analysis: Data were collected and statistically analyzed using repeated measures and ANOVA test to verify the hypothesis and control both within and between variabilities with significance of 0.05. The data collected for both groups before treatment (pre), after 4weeks (12 sessions, (post- 1) and after 8 weeks (24 sessions, (post -2) were compared with each other.

Phase	Frequency (Hz)	Mode of application	Time (Minutes)	Total Energy
Initial	25	Fast Scanning	3	According to the size of each wound (WSA) expressed in (cm^2)
Intermediate	15	Applied at the periphery of the wound *(Fixed points)*	4	
Final	25	Slow Scanning	3	

Tab. I. Treatment protocol of Pulsed High Intensity Nd:YAG laser for wound healing.

1-Results for group (A): The mean value and standard deviation of WSA (cm^2), in group (A) before application of laser (pre) was 8.10±2.35, post-1 was 4.05±1.46 and post-2 was 0.65 ±0.58, there was significant decrease in the WSA after 4 weeks and 8 weeks compared to initial measurement (before treatment), $p>0.05$ as shown in table (2)

2-Results for group (B): The mean value and standard deviation of WSA (cm2), in group (B) at the beginning of the study (pre) was 8.75±2.48, post-1 was 7.75± 2.20 and post-2 was 6.40 ± 2.22, there was decrease in the WSA after 4 weeks and 8 weeks compared to initial measurement (pre), $p>0.05$ as shown in table (2).

3-Comparing the mean values of WSA in group (A) and group (B) before treatment (pre), after 4 weeks (post-1) and after 8 weeks (post-2) we found that before treatment (pre), there were no significant differences between the two groups, $p > 0.05$. After 4 weeks (post-1), there was a significant reduction in WSA in group (A) compared to group (B) ($p < 0.05$). After 8 weeks (post-2), there was a significant reduction in WSA in group (A) compared to group (B), ($p < 0.05$), as shown in figure (1).

DISCUSSION

Delayed wound healing specially in diabetic ulcer is continuing challenge in rehabilitation medicine despite some recent advances in understanding of its basic principles and problems in wound healing that continue to cause significant morbidity and mortality. A great number of studies have been conducted on acceleration of wound healing, attainment of normal breaking strength and prevention of keloid and scar formation by using many physical methods such as therapeutic ultrasound, laser therapy and electrical stimulation [13].

This study was designed to investigate the effect of pulsed high intensity Nd:YAG laser on chronic diabetic foot ulcer. The result of this study showed that, there was significant decrease in WSA in group (A), after 4 and 8 weeks of laser treatment, compared to group (B).

Hawkins and Abrahamse [14] investigated the effect of multiple exposures to Low Intensity Laser Therapy (LLLT) on cell response, using as experimental model wounded skin fibroblasts. They demonstrated that correct energy density or fluency and the number of exposures can stimulate cell response in terms of cell migration and proliferation by stimulating mitochondrial activity and maintaining viability without causing additional stress or damage to the cells. Results indicate that the cumulative effect of lower doses determines the stimulatory effect.

Several indices of tissue repair are positively affected by laser treatment. In vivo studies and clinical reports indicated that laser therapy promotes wound healing by accelerating collagen synthesis [15,16], inflammation course, healing time and strength acquisition [17]. These results are consistent with previous reports that have demonstrated elevation of several metabolic indices of ATP synthesis [18], fibroblast proliferation, [16] and collagen synthesis, as well as increases in the biomechanical indices of tissue healing.

Laser stimulation leads to increased production of ATP from ADP molecules.

Wound Surface Area (WSA cm2)						
Groups	**HILT group (A)**			**control group (B)**		
Time of measurements	pre	Post-1	Post-2	pre	Post-1	Post-2
Mean	8.10	*4.05*	0.65	8.7500	7.7500	6.4000
SD ±	2.35	1.46	0.58	2.48945	2.20347	2.22781
F value (df)	86.46 (2)			242.67 (2)		
P value	P>0.05			P>0.05		

Tab. 2. The WSA for group (A) and group (B) at (pre), (post-1) and (post-2).

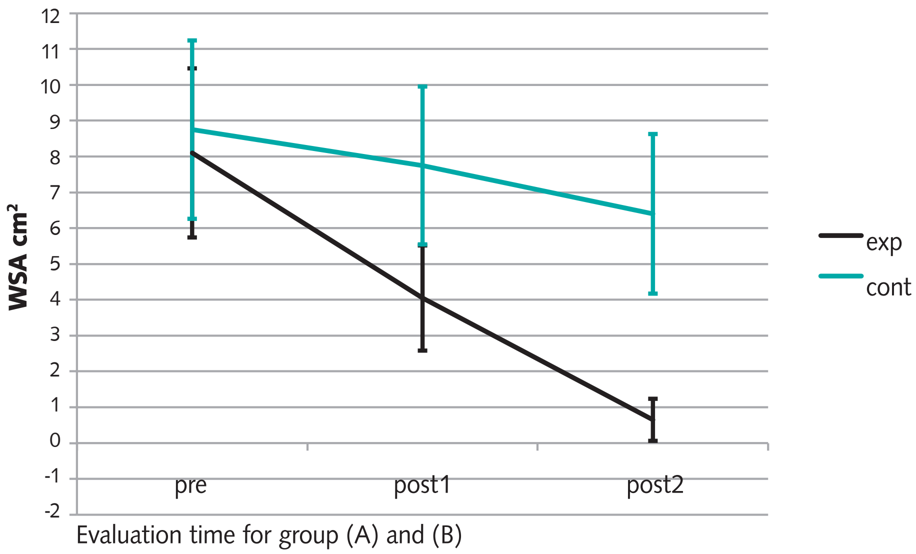


Figure (1): The mean values of WSA for group (A) and (B) at (pre), (post-1) and (post-2)

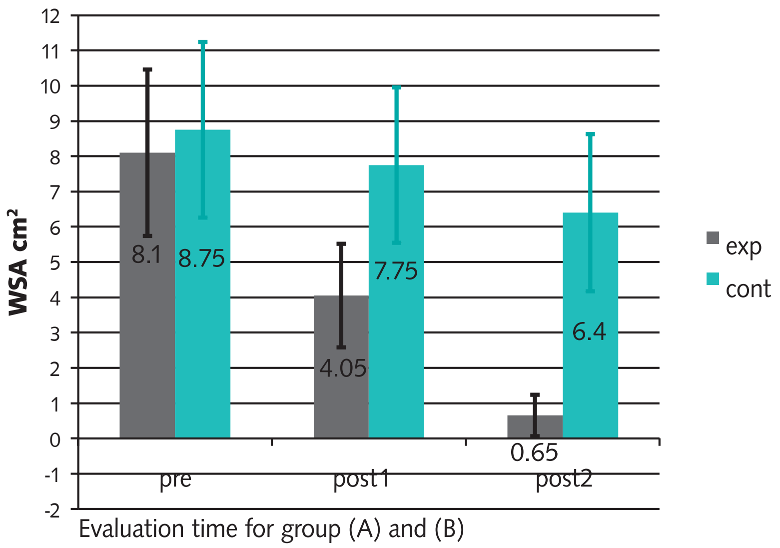


Figure (2): The mean values of WSA for group (A) and (B) at (pre), (post-1) and (post-2)

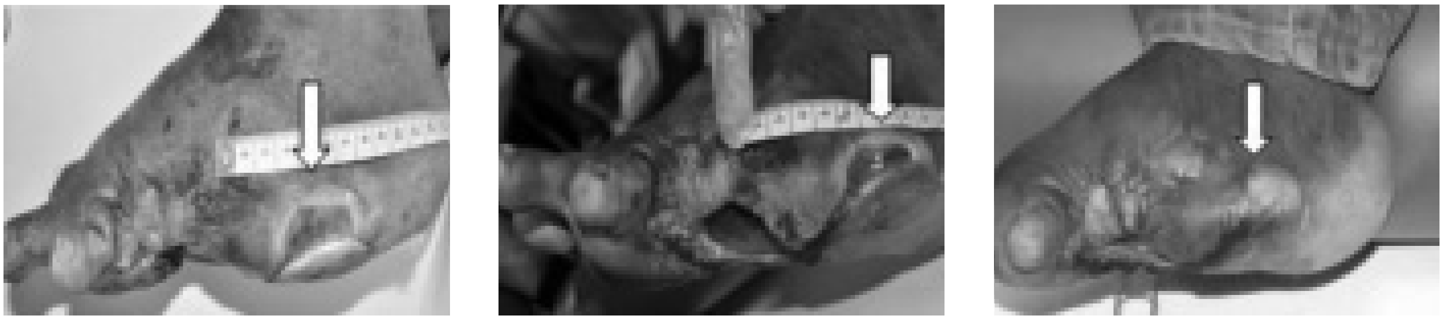
These processes occur in mitochondria, although the mediator between the action of photons and biochemical processes activation has not yet been identified. From numerous experiments and studies in vitro, it is evident that laser light is able to induce cell replication and synthesis of RNA and proteins (eg, collagen), promoting the healing process [19,20].
Our protocol has been designed on the basis of the study of Madrado et al [21], which evaluated the effects of laser therapy in experimental cutaneous wound healing and concluded that a dose of 4 J/cm² was more effective to that of 8 J/cm².
In addition, Hawkins and Abrahams [22,23] reported that a dose of 5 J/cm² generated by a HeNe laser stimulates mitochondrial activity, leading to re-establishment of cellular functions, and induces proliferation and migration of fibroblasts, thus hastening wound closure.
In contrast, a dose of 10 J/cm² was associated with a significant amount of cellular and molecular damage.
Pereira et al [24] studied the effect of a 120 mW GaAs diode laser on fibroblasts, and concluded that a dose of 3 J/cm² stimulated fibroblast proliferation without impairing procollagen synthesis.
Pourzarandian et al [25] studied the effect of Er: YAG laser irradiation on cell growth of cultured human gingival fibroblasts and concluded that the optimal energy density for stimulation was 3.37 J/cm². The results indicate that Er: YAG laser irradiation may benefit wound healing.

It has been reported that in the case the tissues are affected by chronic phatological conditions, longer intervals between treatments are required, with a maximum of two or three sessions/week [26]. Clinical practice has shown that deeper is the wound or target tissue, more treatments are required and, as a general rule, it is better to use 3-4 treatments/week with moderate doses than using higher doses and fewer treatments [27].

In agreement with outcomes of previous studies our results completely support

Figure (3): Differences in wound surface area by using digital camera

Case 1

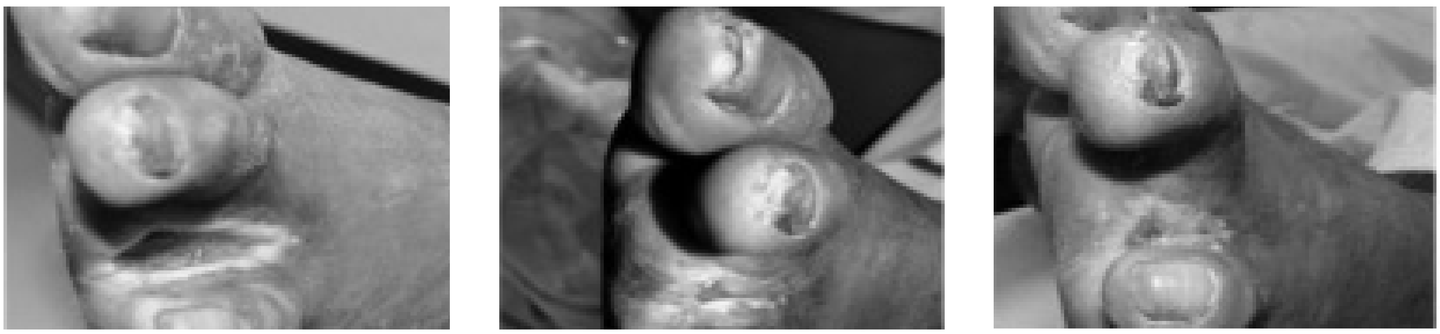


Pre treatment **After 4 weeks** **After 8 weeks** (complete closure)

Case 2

Pre treatment **After 4 weeks** **After 8 weeks (complete closure)**

Case 3



Pre treatment **After 4 weeks** **After 8 weeks** (complete closure)

the hypothesis that healing process of diabetic foot ulcer is favoured by pulsed high intensity Nd:YAG laser. In fact the findings show that the application of pulsed high intensity Nd:YAG laser, according with the described protocol, is safe and effective for the treatment of grade 2 chronic diabetic foot ulcer, and induces a significant decrease in WSA as demonstrated by evaluation of the wounds at 4 and 8 weeks.

CONCLUSION

The common lower extremity problem associated with diabetes is the development of foot ulcers. The delayed ulcer healing and its effects on the rate of recovery and period of hospitalization are serious and functional problems. Therefore the selection of the appropriate treatment modalities is one of the big challenges to deal with those patients and the rehabilitation teams. The findings of this study are important to the specialists who work in the field of physical therapy and rehabilitation because suggest advanced physical therapy modalities in treating one of the most complicating problems with diabetic patients. The advantages to develop new strategies and standardize protocols for treating diabetic foot ulcer result in decrease of cost and faster time of wound healing.

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