Low Level Laser Therapy and Diabetic Peripheral Neuropathy
Influence of low level laser therapy versus pulsed electromagnetic field on diabetic peripheral neuropathy

Abstract

Background: Peripheral neuropathy is a common complaint of diabetes, leading to pain and reduced motor nerve conduction velocity. Clinical symptoms of peripheral neuropathy are present in approximately 25% of diabetic individuals, while nearly all diabetics have a reduction of nerve conduction velocity.

Purpose: This study aimed to evaluate and compare the effect of low-level laser therapy (LLLT) versus pulsed electromagnetic field (PEMF) on pain intensity and motor nerve conduction velocity (MNCV) in patients with diabetic neuropathy.

Methods: Thirty patients with type II diabetes suffering from diabetic peripheral neuropathy, participated in this study for 4 weeks (3 sessions/week), and were chosen randomly from the diabetes and endocrine institution. Patients were randomized equally into two groups: Group A (LLLT group): received LLLT for lower extremities for 12 sessions at a frequency of 3 sessions/week. Group B (PEMF): received pulsed electromagnetic field for 12 sessions at a frequency of 3 sessions/week.

Results: At the end of the study; there was non-significant difference between two groups post-study in pain level where P-values was (0.606). There were no significant differences between two groups in amplitude, distal latency and MNCV of RT side post-study, where P-values were (0.082), (0.911) and (0.342) respectively. There were no significant differences between two groups in amplitude, distal latency and MNCV of LT side post-study, where P-values were (0.265), (0.550) and (0.334) respectively.

Conclusions: The study findings indicate that both LLLT and PEMF could be effective therapeutic modalities in the treatment of painful diabetic neuropathy in that they are able to modify pain, and some electrophysiological parameters of peripheral nerve function.

Keywords: Low-level laser therapy, Pulsed electromagnetic field, Neuropathy, Diabetes

Introduction

One of the most common complications of diabetes mellitus is painful diabetic neuropathy (PDN). Within 10 to 15 years of diabetes approximately 50% of patients will develop PDN [1]. In neuropathy, there is a progressive degeneration of the peripheral nerves in the lower limbs especially, that leads to sensory and motor deficits [2]. Diabetic peripheral neuropathy (DPN) is a frequent complication of diabetes that affects up to 50% diabetic patients in the United States [3,4]. It is a major cause of morbidity and increased mortality, and is associated with duration of diabetes, hyperlipidemia, and poor glycemic control [4]. Diabetic polyneuropathy affects both large and small sensory afferent nerve fibers. Conduction velocities in motor nerves reduced in patients with diabetic neuropathy [5]. Studies showed that large fiber involvement (group Ia) polyneuropathy and abnormal muscle spindle innervations can lead to lose lower extremities proprioception as ankle position sense, decreased tactile sensitivity and ankle vibratory sense that are responsible for maintaining postural stability and walking [6]. Diabetic polyneuropathy also affected small
nerve fibers that responsible for pain and temperature sense causing decreased sensory nerve conduction velocity [7].

In many patients with diabetic neuropathy, pain will develop as a symptom, affecting up to 30% of the diabetic population; symptoms are localized to the lower extremities, primarily the soles and toes [8]. In addition to discomfort, all areas of patients' lives including sleep, mood, mobility, ability to work, interpersonal relationships, overall self-worth, and independence, are affected [9].

Current therapy for DPN is purely symptomatic, aiming to relieve the pain through the administration of various analgesic drugs. These drugs are effective, but no more than 40–60% of patients show adequate symptomatic relief. Moreover, these drugs are frequently associated with central nervous system side effects and do not slow the progression of the underlying neuropathy [10]. The efficacy of most conservative treatment options for painful diabetic neuropathy is still little known. Among the different options for treatment, low-level laser therapy (LLLT) may have the potential to induce a biostimulatory effect on the nervous system [11, 12]. Because the typical etiology of peripheral neuropathic pain starts with injury to a peripheral nerve, the great majority of research into the treatment of neuropathic pain is focused predominantly on the nerves themselves. Several clinical and experimental research studies on peripheral nerve injuries used LLLT because it promotes microcirculation in the irradiated area; increases nerve functional activity increases the rate of axon growth and myelination and improves regeneration of the injured nerve [13, 14]. In addition, low-power laser has also been employed for the treatment of other diabetic complications, such as foot ulcers [15], diabetic microangiopathy [16, 17] and wound healing [18]. Also, it has been shown that regular exercise with or without dietary intervention and/or oral blood glucose-lowering medication has benefits in patients with Type 2 diabetes [19, 20].

One of the approaches which is currently of clinical interest includes pulsed electromagnetic fields (PEMF), which have analgesic, neurostimulatory, trophic, and vasoactive actions [21]. PEMF treatment has the potential to modulate neuropathic pain and nerve impulse. It may be due to decrease in endoneural hypoxia, perineural edema, ischemia of peripheral nerves, and improved microcirculation that leads to positive changes after treatment sessions [22].

The problem of nerve damage in diabetes is one of the most neurological and metabolic diseases, which is still over looked by scientists [23]. The nerve damage of polyneuropathy lies in a gray zone; it is equally attributed to both mild segmental demyelination and axonal degeneration [24].

To our knowledge, no study has yet compared magnetic field therapy (which has limited research supporting its use), and LLLT (which is among the most common treatments for diabetic neuropathy), in patients with diabetic neuropathy. Thus, our aim was to investigate which modality gives better results in treating diabetic neuropathy.

Material and methods

Subjects

A total of 30 patients with type II diabetes suffering from diabetic peripheral neuropathy, participated in this study for 4 weeks (3 sessions/week), and were chosen randomly from the diabetes and endocrine institution for this study. Eligible patients included (20 women and 10 men), ranging in age from 40 to 60 years with a mean of (47.5±2.38) years. The patients had longstanding type 2 diabetes associated with painful peripheral neuropathic symptoms for more than 6 months involving both lower extremities and complained of burning pain with paresthesia in both legs. Neurological examination of the patients revealed sensory abnormalities in both lower extremities. Patients were excluded from the study if they had unstable glycemic control and/or medical conditions that would confound assessment of neuropathy such as malignancy, active/untreated thyroid disease, peripheral vascular diseases (PVD), vascular insufficiency, significant renal or hepatic disease, pregnancy and nerve damage as a result of prior reconstructive or replacement knee surgery, back surgery, spinal stenosis, spinal compression or radiculopathy. Patients were randomly assigned equally into two groups each group included 15 patients. **Group A (LLLT group):** received LLLT for lower extremities for 12 sessions at a frequency of 3 sessions/week. **Group B (PEMF group):** received PEMF for 12 sessions at a frequency of 3 sessions/week. The randomization was done by a colleague independent and blind to the study who took a sealed opaque envelope from a box following a numerical sequence; within which the group description was randomly placed within them.

Instrumentation

Assessment Instrument

**Visual Analog Scale**

It was used to measure the intensity of pain pre and post treatment. It is a vertical or horizontal line graduated by different levels of pain starting from (0 - no pain) till (10- worst pain). The VAS is a reliable and valid tool for the quantification of perceived pain [25].

Electromyography Device for Nerve Conduction Studies

The measurement of peroneal motor conduction velocity (P MCV), amplitude and distal latency was measured by using Computerized Electromyography TonniesNeuroscreenPlus Version 1.59 (1998; Erich Jaeger GmbH, Hoechberg, Germany).

Treatment Instrument

**Laser Scanner device**

Italy ASA Co., Bravo Style of laser used in this study. It produces combined irradiation of He-Ne and infrared laser. The device emits both helium-neon and infra-red laser in a mixed light. He-Ne wave length was 632.8 nm, continuous. Infra-red wave length was from 780-905 nm, pulsed this device discharges a uniform irradiation of the relatively large areas in a carefully
controlled and prescribed manner. Infrared Laser applied on both feet for twenty minutes using frequency of 150 Hz wave length of 905 nm and an average power of 0-60w, with energy density of 3.6 joules/cm².

**Pulsed electromagnetic field**
Using ASA magnetic field for magneto therapy, its model is Automatic PMT Quattro PRO. The appliance must be connected to electrical mains supplying 230 v 10% at a frequency of 50 or 60 Hz with earth connection. The frequency of output magnetic impulses ranged from 0.5 up to 100 Hz, and the intensity was displayed in percentage ranged from 5% to 100% of the maximum layout of the solenoid used. The intensity and spatial layout of the generated magnetic field of the appliance varied according to the type solenoid used whether for trunk, limb or Transcranial.

**Evaluative Procedure**

**Pain Assessment**
The level of pain was assessed by using VAS, the patient was asked to determine the level of his/her pain on 10 cm scale as (0 = no pain) and (10=worst pain) by drawing a line corresponding to the intensity of pain. Assessment of pain was done before starting the program of treatment and after compliance of all treatment sessions.

**Electrophysiological Assessment**
Conventional NCSs were administered using a standard testing protocol. Studies included testing of bilateral peroneal MCV, amplitude and distal latency. All measurements were done under standard room temperature of 25°C. The skin temperature of the leg was maintained at 37°C. Procedure of nerve conduction velocity measurement. The patients were positioned supine. An active electrode was placed over the midpoint of the extensor digitorum brevis muscle on the dorsum of the foot. Reference electrode was placed slightly distal to the fifth metatarsal phalangeal joint. Ground electrode placement was over the dorsum of the foot. Stimulation point 1 (S1): the cathode was placed 10 cm proximal to the active electrode, slightly lateral to the tibialis anterior tendon. Stimulation point 2 (S2): the cathode was slightly posterior and inferior to the fibular head. The anode was proximal. Pulse duration of 0.2ms at the rate of 1/s at supramaximal intensity was used for conduction studies. The distance between S1 and S2 was measured by tape measurement and entered into the computerized electromyography device. The device automatically calculates the motor conduction velocity [26].

**Treatment Procedure**

**Low Intensity Laser Therapy (LLLT)**
Patient was placed in supine lying, fully relaxed and supported position. The area of laser application on the leg and foot was washed by alcohol. The laser scanner was applied perpendicular on the area of laser application. The laser beam was adjusted to cover the area of application in width and length from the malleoli till tip of the big toes. Infrared Laser applied on both feet for twenty minutes using frequency of 150 Hz wave length of 905 nm and an average power of 0-60w, with energy density of 3.6 joules/cm² [27].

**Pulsed Electromagnetic Fields**
Pulsed electromagnetic fields (ASA Easy terza series; Italy) was used in the treatment of group A only. Each patient was placed in a comfortable relaxed position (supine position). The appliance was connected to electrical mains supplying 230 V. The solenoid was adjusted to be over the lower limb, with frequency of 50 Hz and intensity of 20 G for 20 min. Treatment was conducted for 4 weeks, three times per week, day after day [28].

**Statistical Analysis**
Statistical analysis was performed using SPSS software (version 16.0). Data were expressed as mean ± standard deviation (SD). Mean changes within groups (pre and post-study) were analyzed using Paired T-test while mean changes between groups (pre and post-study) were analyzed using unpaired T-test to test hypothesis between groups. The level of significance was set at p<0.05.

**Results**
This study was concerned with comparison between the effect of PEMF versus LLLT on pain intensity and motor nerve conduction velocity (MNCV) in patients with diabetic neuropathy. Thirty subjects were assigned randomly into two equal groups.

**Group (A):** Fifteen subjects received LLLT for lower extremities. The data in Table 1 represented, their mean age (47.5±2.38) years, weight (74.2±2.7) kg and height (162.1±2.08) cm.

**Group (B):** Fifteen subjects received PEMF. The data in Table 1 represented, their mean age (46.33±1.29) years, weight (76±2.5) kg and height (161.5±1.6) cm. There was no significant difference between two groups in their mean age, weight and height, where P-values were (0.098), (0.071) and (0.379) respectively.

**Pre study means values within both groups**
As shown in Table 2, the mean values and SD of pain for groups (A and B) before the study were (7.8±0.86), (7.66±1.17)
Comparison of pre and post study for group A
As shown in Table 4, the mean values and SD of pain for group A pre and post-study was (7.8 ± 0.86) and (2 ± 0.53) respectively. The mean values and SD of amplitude of RT side for group A pre and post-study were (1.32 ± 0.278) and (1.85 ± 0.388) respectively and for LT side were (1.11 ± 0.44) and (1.83 ± 0.54) respectively. The mean values and SD of distal latency of RT side for group A pre and post-study were (6.08 ± 0.598) and (2 ± 0.53) respectively. The mean values and SD of amplitude of RT side for group A post-study were (7.66 ± 1.17) and (2.04 ± 0.48) respectively and for LT side were (6.66 ± 0.64) and (4.61 ± 0.602) respectively. The mean values and SD of MNCV of RT side for group A post-study were (40.68 ± 2.83) and (42.92 ± 1.97) respectively and for LT side were (38.5 ± 4.82) and (42.7 ± 3.13) respectively. There were significant differences between pre and post-study in all measured variables, where P-values were (0.000).

Comparison of pre and post study for group B
As shown in Table 5, the mean values and SD of pain for group B pre and post-study was (7.66 ± 1.17) and (2 ± 0.53) respectively. The mean values and SD of amplitude of RT side for group B pre and post-study were (1.43 ± 0.286) and (2.1 ± 0.383) respectively and for LT side were (1.5 ± 0.48) and (2.04 ± 0.48) respectively. The mean values and SD of distal latency of RT side for group B pre and post-study were (6.05 ± 0.68) and (4.83 ± 0.49) respectively and for LT side were (5.66 ± 0.64) and (4.61 ± 0.602) respectively. The mean values and SD of MNCV of RT side for group B pre and post-study were (40.68 ± 2.83) and (42.92 ± 1.97) respectively and for LT side were (39.11 ± 3.52) and (42.5 ± 2.26) respectively. There were significant differences between pre and post-study in all measured variables, where P-values were (0.000).

Discussion
Diabetic peripheral neuropathy is the presence of symptoms or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes [29]. It represents 60% of people with diabetes, confers the greatest risk of foot ulceration [30,31]. Neuropathy causes loss of protective sensation and loss of co-ordination of muscle groups in the foot and leg that lead to increase mechanical stresses during ambulation [32,33].
Table 4. Pre-study post-study mean values of measured variables for group A.

<table>
<thead>
<tr>
<th>Items</th>
<th>Pre-study Mean ±SD</th>
<th>Post-study Mean ±SD</th>
<th>% of change</th>
<th>t-value</th>
<th>p-value</th>
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<tr>
<td>Pain level</td>
<td>RT 7.8±0.86</td>
<td>LT 2.1±0.33</td>
<td>74.4 %</td>
<td>29</td>
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<td></td>
<td>Amplitude RT 1.32±0.278</td>
<td>LT 1.85±0.48</td>
<td>40.2 %</td>
<td>-7.78</td>
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<td>Distal latency RT 6.08±0.598</td>
<td>LT 5.87±0.74</td>
<td>-21 %</td>
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<tr>
<td></td>
<td>MNCV RT 40.68±2.83</td>
<td>LT 42.92±1.97</td>
<td>5.5 %</td>
<td>-4.33</td>
<td>0.000</td>
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Table 5. Pre-study post-study mean values of measured variables for group B.

<table>
<thead>
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<th>Items</th>
<th>Pre-study Mean ±SD</th>
<th>Post-study Mean ±SD</th>
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<tr>
<td>Pain level</td>
<td>RT 7.66 ± 1.17</td>
<td>LT 2.1 ± 0.833</td>
<td>-72.6 %</td>
<td>41.5</td>
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<tr>
<td></td>
<td>Amplitude RT 1.43 ± 0.286</td>
<td>LT 2.1 ± 0.383</td>
<td>46.9 %</td>
<td>-7.08</td>
<td>0.000</td>
</tr>
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<td></td>
<td>Distal latency RT 6.05 ± 0.68</td>
<td>LT 4.83 ± 0.49</td>
<td>-20.2 %</td>
<td>8.56</td>
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<td></td>
<td>MNCV RT 41.07 ± 2.79</td>
<td>LT 43.59 ± 1.79</td>
<td>6.1 %</td>
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Diabetic peripheral neuropathy is estimated to occur in 50–90% of individuals with diabetes for more than 10 years [34]. The impairment of peripheral nerve function in diabetic individuals should be regarded not as a neurological complication but as a neurological manifestation of the disease [35,36] as it approaches 50% in most diabetic population, mainly with painful symptoms [37]. Treating neuropathy is a difficult task for the physician and most of the conventional pain medications primarily mask symptoms [38,39] and have significant side effects and addiction profiles. So, the aim of our study is evaluating the effects of LLLT versus PEMF on pain intensity and motor nerve conduction velocity (MNCV) in patients with diabetic neuropathy. The present study showed that both PEMF and LLLT improved amplitude, distal latency and bilateral peroneal MNCV. Also, the study results, demonstrating significant pain relief in all patients in both groups. Comparative analysis showed non-significant differences between group A and B after treatment.

The improvement of electrophysiological parameters (peroneal MCV, amplitude and distal latency) in the Laser group could be explained as follows; laser has a biostimulatory effect on the nervous system [40]. Earlier research findings suggested that LLL treatment appears to enhance reinnervation of target tissues subsequent to nerve injury [41]. Rochkind [42] found that laser improves function recovery and recruitment of voluntary muscle activity through application transcutaneously to the site of nerve injury (15 min) and to the corresponding segments of the spinal cord (15 min).

The other studies concluded that laser irradiation prevents motor cell degeneration, induces Schwann cell proliferation, allows higher neural metabolism, and increases myelination and axon regeneration [14,43]. NCS is known as the gold standard for diagnosis of neuropathy, and it is correlated with disease severity [44]. In this study, we used NCS in order to objectively evaluate the effect of LLLT in the treatment of distal symmetric diabetic polyneuropathy. The exact mechanism by which LLLT improves NCV is largely unknown. However, several theories may help explain the enhanced conduction velocity observed here. Laser radiation has been shown to change cell and tissue function [45]. It has been suggested that irradiation activates collagen synthesis, varies DNA synthesis [46], improves the function of damaged neurological tissue [47], reduces inflammation, and relieves pain [48].

Despite the previous observations by Zinman et al. [49], and Peric et al. [50], who reported that current results do not provide sufficient evidence to recommend LLLT for pain symptoms in polyneuropathy, this study clearly demonstrated a significant positive effect of LLLT on improvement of nerve conduction velocity on distal symmetric polyneuropathy. In our study, objective criteria based on NCS was positively correlated with the therapeutic potential of LLLT.

Patients receiving LLLT had a decrease of pain level through four weeks of treatment. It was reported that LLLT improve local microcirculation and it can also improve oxygen supply to hypoxic cells and at the same time it can remove the collected waste products [51]. In the cases of neuropathic...
Pain, the analgesic effects of LLLT may be due to the local release of neurotransmitters such as serotonin, increased mitochondrial ATP production, increased release of endorphins, or anti-inflammatory effects. The mechanism whereby LLLT relieves pain is unknown [52].

PEMF group showed improved peroneal nerve distal latency and nerve conduction velocity (NCV) that can be attributed to fewer studies suggested that endoneurial capillaries in peripheral nerves of the diabetes are thickened [53] and perineurial basement membrane are widened [54]. A permeability disorder at the blood nerve or blood perineurial barrier in diabetics could lead to endoneurial metabolic derangements, however possibly resulting in neuropathy. PEMF by targeting at increased circulation and anti-inflammatory effects combined with the pain relief and restoration of normal nerve conduction lead to reversal of the damage that cause the peripheral neuropathy. Recently, it has been observed that PEMF modulates the neurite growth in vitro and nerve regeneration in vivo, which further explains the improvement obtained in results of group B.

In the available literature, there is limited research on PEMF treatment for diabetic peripheral neuropathy; nevertheless, a few studies support the current findings. In such studies, study of PEMF [55] directed to investigate the effect of PEMF on pain and motor nerve conduction velocity (NCV) in patients with diabetic neuropathy revealed significant reduction of pain intensity and significant improvement of peroneal nerve conduction velocity (m/s).

Previous studies had reported that PEMFs are able to modify some parameters of nerve function in diabetic patients and can stimulate nerve growth, regeneration, and functional recovery of nerves in cells in animal models with nerve disease [56,57].

The effects of PEMF are to trigger a biologic response such as cell proliferation that represents the basic effect to explain some relevant results. It enhances nerve regeneration and accelerates recovery in experimentally divided and sutured peroneal nerve which can improve number of nerve fiber and thereby amplitude achieved in nerve conduction study [58].

Application of PEMF facilitates regression of the main clinical symptoms of DPN, improves the conductive function of peripheral nerves, improves the state of 1a afferents, and improves the reflex excitability of functionally diverse motor neurons in the spinal cord. This explanation is supported by Musaev et al. [59] who performed a clinical and electro neuromyographic study in 121 patients with diabetic polyneuropathy before and after the courses of treatment with PEMFs at different frequencies (100 and 10 Hz). The study concluded that PEMF at 10Hz was found to have therapeutic efficacy, especially in the initial stages of DPN and in patients with DM for up to 10 years.

The reduction of pain intensity was better after treatment of PEMF, and this result is in agreement with Morki and Sinaki [60] who postulated that magnetic therapy has become one of the most rapidly emerging alternative therapies where magnets have been promoted for their analgesic and energizing effects with no adverse effects unlike drugs. The analgesic effect of PEMF therapy could be attributed to the physiologic mechanisms of pain relief, which may be owing to presynaptic inhibition or decreased excitability of pain fibers [61].

Moreover, PEMF can modulate the action of hormones, antibodies, and neurotransmitter surface receptor sites of a variety of cell types. This may cause changes in transfer rate of electrons during the electron exchange between single molecules that may either slow down or accelerate chemical reactions [62].

The pain is most likely to arise from increased activity of injured small – diameter regenerating fibers, [63] which fire rapidly and at abnormally low thresholds [64]. The PEMF influence diabetic neurons and cell membrane of cutaneous nociceptors thereby inducing change in the cellular [65] and pericellular microenvironment [66,67].

Conclusions
The study findings indicate that LLLT and PEMF could be an effective therapeutic modality in the treatment of painful diabetic neuropathy in that they are able to modify pain, and some electrophysiological parameters of peripheral nerve function. Further studies would be worthwhile because diabetic neuropathy is a disorder with multiple symptoms which affects function, produces pain, autonomic involvement and future studies can consider functional improvements, pain threshold, Assessing sensory and motor impairment.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions

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