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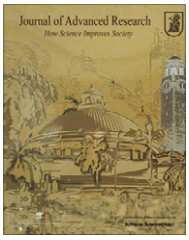

ORIGINAL ARTICLE

Effect of low level laser therapy on neurovascular function of diabetic peripheral neuropathy

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KEYWORDS

Diabetic peripheral neuropathy;
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Skin microcirculation

Abstract Diabetic neuropathy is the most common complication and greatest source of morbidity and mortality in diabetic patients. Thirty male and female patients with painful diabetic neuropathy and abnormal results from nerve conduction studies participated in this study. Their ages ranged from 45 to 60 years with a mean of 52.1 ± SD 4.7 years. Patients were randomly assigned into two equal groups of 15, an active laser group (laser group) and a placebo laser group (control group). The laser group received scanning helium neon (He–Ne) infrared laser with wavelength 850 nm and density of 5.7 J/cm^2, applied to the lumbosacral area and the plantar surface of the foot for 15 min each site/session three times per week for four weeks (i.e. 12 sessions). Pain intensity via visual analogue scale, bilateral peroneal motor nerves, sural sensory nerves conduction velocity and amplitude and foot skin microcirculation, were measured pre- and post-treatment for both groups. Pain was significantly decreased ($p \leqslant 0.05$) and electrophysiological parameters and foot skin microcirculation were significantly improved ($p \leqslant 0.05$) in the laser group, while no significant change was obtained in the control group. Low level laser therapy within the applied parameters and technique could be an effective therapeutic modality in reducing pain and improving neurovascular function in patients with diabetic polyneuropathy.

Introduction

Diabetic peripheral neuropathy (DPN) is frequently the most common microvascular complication of both type I and II diabetes; it is thought to be progressive and irreversible [1]. Diabetic neuropathy is a consequence of peripheral nerve injury derived from microangiopathy of the vasa nervorum, loss of axons and axonal atrophy as a result of the combination of different mechanisms of tissue damage [2]. All nerve fibres may be injured but small myelinated and unmyelinated fibres that conduct pain and temperature are most affected [3]. Not only does the nerve die, but the repairing mechanisms of nerve regeneration are also

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defective [1]. In association with neuropathy, disturbed microcirculation is responsible for the development of diabetic gangrene, ulcers, and infections of skin and bone in long-standing diabetic patients [4]. In many patients with diabetic neuropathy, pain will develop as a symptom, affecting up to 30% of the diabetic population; symptoms are localised to the lower extremities, primarily the soles and toes [5]. 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 [3].

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 [6]. Non-pharmacological symptomatic treatments have also been proposed, including acupuncture [7], near-infrared phototherapy [8], low-intensity laser therapy [9,10], static and pulsed magnetic field therapies [11,12], and various electrotherapies, including transcutaneous electrical nerve stimulation (TENS) [13], percutaneous electrical nerve stimulation [14] and spinal cord electrostimulation [15]. 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 biostimulational effect on the nervous system [16,17]. Because the typical aetiology 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 myelinization and improves regeneration of the injured nerve [18–21]. In addition, low-power laser has also been employed for the treatment of other diabetic complications, such as foot ulcers [22], diabetic microangiopathy [4,23] and wound healing [24]. Therefore the purpose of this study is to evaluate the effect of LLLT on pain intensity, motor and sensory nerve conduction velocity (NCV), and foot skin microcirculation, in patients with painful diabetic neuropathy.

Subjects and methods

Subjects

A total of 30 patients with painful DPN were referred from the diabetic clinic in El Kasr EL Einy Hospital and the neurological outpatient clinic of the Faculty of Physical Therapy, Cairo University, with a diagnosis of peripheral neuropathy confirmed by an abnormal nerve conduction study. Eligible patients included (20 women and 10 men), ranging in age from 45 to 60 years with a mean of 52.1 ± SD 4.7 years. The patients had longstanding type 2 diabetes associated with painful peripheral neuropathic symptoms for $\geqslant$6 months (11.9 ± 3.1) duration 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 (claudication, skin discoloration, ulceration), significant renal or hepatic disease, pregnancy, alcohol or illicit drug abuse, nerve damage as a result of prior reconstructive or replacement knee surgery, back surgery, spinal stenosis, spinal compression or radiculopathy (sciatica), nonambulatory status, an ankle brachial index (A/B index) below 0.9, and other neurologic diseases. This study was approved by the Ethical Committee of the Faculty of Physical Therapy, Cairo University. The study procedures were explained and informed consent was obtained from eligible participants. Patients were randomly assigned equally into an active laser group (laser group) and a placebo laser group (control group). The use of analgesic or adjuvant analgesic medications (e.g. opiates, antidepressants, anticonvulsants, local anesthetics) was allowed but had to be unchanged for at least four weeks before entering the study and during the study.

Instrumentation

Assessment instrument

Visual analog scale

VAS was used to assess the intensity of perceived pain. The VAS is a reliable and valid tool for the quantification of perceived pain [25].

Electroneurography device

The Toennis Neuroscreen Plus device was used to measure peroneal motor conduction velocity (P MCV), amplitude and sural sensory conduction velocity (S SCV) and amplitude.

Laser Doppler flow meter

The Peri Scan System was used to measure skin microcirculation of feet at three different points of plantar surface [26]. Laser Doppler perfusion imaging is a reliable method for characterizing microvascular changes in the human skin [27].

Treatment instrument

The Laser Scanner device (Italy ASA Co., Bravo Style), which emits both He–Ne and infrared laser in a mixed light, was used in the study. He–Ne was continuous with wavelength 850 nm, while infra red was pulsed with wavelength 905 nm. The device had maximum power of 10 W. The output of the device was calibrated at each frequency with a power meter (Omega Laser Systems), and an I.R. Laser Detection Card.

Procedure

Medical history, demographics, physical and neurologic examination were initially performed for all patients. Pain intensity, peroneal and sural nerve conduction studies (NCSs), and foot skin microcirculation, were measured in all participants on both lower limbs upon entry into the study and after four weeks of the treatment.

Assessment procedure

Pain intensity

In VAS, the patient was given a 10-cm line and asked to draw on the line the intensity of pain he was feeling. The left end of the line represented "no pain at all," and the right end of the line represented the "worst pain you can imagine." The patient's mark on the line was measured (in centimetres) with a ruler.

Macrocirculation assessment

Macrocirculation was measured along the main leg arteries, both tibial and peroneal, by using Nicolet Vasoguared to measure the A/B index and detected any PVD and excluded those patients that had an A/B index below 0.9.

Microcirculation assessment

On the occasion of each measurement, the patient was in an acclimatized room with a stable temperature of 22–24 °C and allowed to rest on the back in a recumbent position with both feet supported on a pillow for at least 20 min prior to blood flow measurements. The laser was placed to scan the entire plantar surface of both feet till the complete image of the feet was shown on the screen. Three points of measurement (big toe, little toe and heel) were encircled and the mean value of microcirculation in these areas was measured and the results expressed as perfusion flux units. All measurements were performed with a skin temperature at 37 °C.

Electrophysiological assessment

Conventional NCSs were administered using a standard testing protocol. Studies included testing of bilateral peroneal MCV and amplitude and sural SCV and amplitude. All measurements were done under standard room temperature of 25 °C. The skin temperature of the leg was maintained at 37 °C.

Peroneal nerve MCV was measured with standard surface electrodes with stimulation distally about 8 cm proximal to the active pickup electrode, just lateral to the Tibialis anterior tendon; proximal stimulation was applied just below the head of the fibula, with the recording electrode over the Extensor Digitorum Brevis and the earth electrode positioned mid-calf [28].

Sural nerve SCV was measured with the active pickup electrode placed posterior and below the lateral malleolus of the fibula; the reference electrode was placed 3 cm distal to the active electrode and the earth electrode positioned between the cathode of the stimulator and the active pickup electrode. Stimulation was applied slightly lateral to the midline in the lower third of the posterior aspect of the leg with the cathode distally about 17 cm from the active electrode [28].

Treatment procedure

Helium neon (He–Ne) infrared laser (850 nm,) in continuous wave (CW) mode was used for treatment in both groups. The instrument had 25 pre-stored programmes including a programme for DPN. The patient lay in comfortable prone position. The distance between the laser head and the treated area (height) was fixed accurately at 30 cm. The area of treatment included the whole plantar surface of the foot and the lumbo-sacral area. The *X–Y* dimensions of the lumbo-sacral area was marked by four points, one on the L2, one on the S1 and two points laterally to the spine by about 2 cm, see Fig. 1. These two areas were exposed to LLLT through a sweeping computerized scanning at an angle of 30 ± 15° for 15 min at each site. Before laser application, the target areas were cleaned with alcohol (95%) to minimize any backscatter or reflection from oily skin. According to the pre-stored programme for DPN, the instrument automatically delivered 5.7 J/cm^2 at an automatically measured therapy time. For protection from the laser's beam, both the subject and the physiotherapist wore protective glasses. The same procedures were taken for the control group with the laser device OFF. As there is no heating effect of laser and the patient was lying prone, the patient could not detect if the device was ON or OFF. Each patient received 12 treatment sessions at a rate of three sessions per week. Both groups were treated under the same conditions, and the patients were treated individually to avoid influencing one another.

Statistical analyses

All data are expressed as mean ± SD. Statistical significance was evaluated by two tailed Student's *t* test (for paired and unpaired values). Analyses were performed using GraphPadPrism, Version 3.0 (GraphPad Software; San Diego, CA, USA) on a personal computer. The significance was set at $p \leqslant 0.05$. The sample size was calculated based on previous studies [9,10]. A power analysis with $\alpha = 0.05$ and power = 80% chance determined that a group size of 15 was adequate to demonstrate a 25% change in the nerve conduction study results as between the groups.

Results

This study was conducted on 30 patients with painful DPN. Fifteen patients were treated with LLLT and another 15 were treated with a placebo laser for four weeks. The demographic profile of the patients is shown in Table 1. At baseline, there were no statistically significant differences in age, duration of diabetes, duration of neuropathy and pain intensity between the two groups.

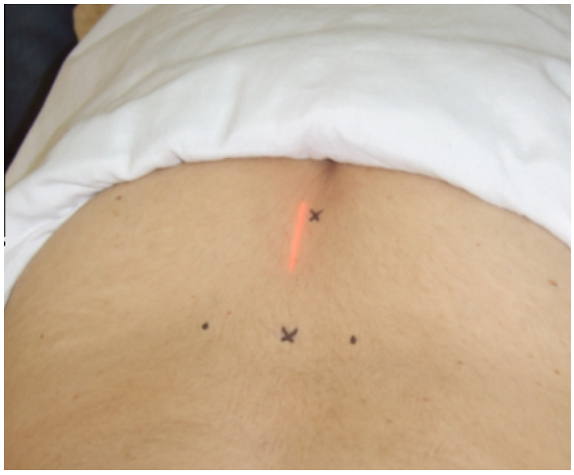

Fig. 1 Application of laser on lumbo-sacral area.

Table 1 Demographic characteristics of patients.

Variables	Groups	Mean ± SD	MD	t	*p*-Value
Age (years)	CG	51.2 ± 5.69	1.93	1.114	0.2[a]
	LG	53.13 ± 3.56			
Duration of diabetes mellitus (years)	CG	11.66 ± 3.8	0.6	0.4861	0.6[a]
	LG	12.26 ± 2.9			
Duration of neuropathy (months)	CG	11.73 ± 0.51	0.27	1.367	0.18[a]
	LG	12 ± 0.57			
Sex n (male/female)	CG	5/10	–	–	1[a]
	LG	5/10			
Pain level intensity	CG	7.2 ± 0.77	0.13	0.61	0.61[a]
	LG	7.33 ± 0.61			

SD: Standard deviation. MD: Mean difference. CG: Control group. LG: Laser group.
[a] Non-significant.

Electrophysiological results

At pre-treatment measurement, no significant difference was found between the groups for either NCV or amplitude of peroneal nerve, see Table 2. Sural nerve response was absent in 73% patients of the two groups and present in 27% of all patients but with abnormal values (reduced SCV and amplitude). In post-treatment measurement, sural SCV was present in 100% of patients in the laser group and it was still absent in the control group.

As regards NCV, in the Laser group, the peroneal and sural nerve conduction was increased significantly ($p = 0.001$ and 0.0001, respectively); there was no significant change in the control group ($p = 0.09$ and 0.07, respectively), see Table 2. Comparing the post-treatment results of the two groups, no significant difference was found for peroneal MCV ($p = 0.1$), but there was a highly significant difference for sural SCV in favour of the Laser group ($p = 0.0001$), see Fig. 2.

As regards the mean amplitude of the peroneal and sural nerve action, potential was increased significantly in the laser group ($p = 0.002$ and 0.0001, respectively), with no significant change in the control group, see Table 2. In post-treatment measurement, no significant difference was found between the groups for peroneal nerve amplitude; there was a highly

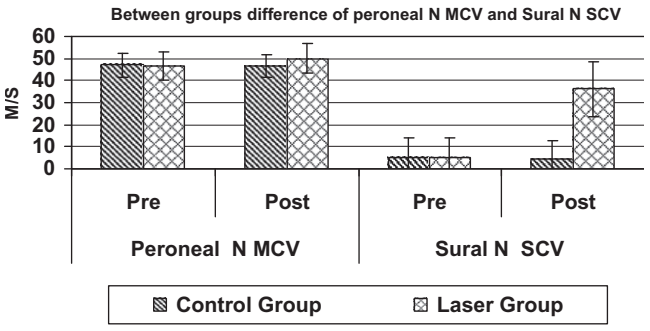

Fig. 2 Comparison of the pre- and post-treatment values (mean ± SD) of NCV between the groups.

Table 2 Electrophysiological values of the groups pre- and post-treatment.

Variables	Groups		Pre M ± SD	Post M ± SD	*t*	*p*-Value
Peroneal nerve MCV (M/SEC)	CG		47.1 ± 5.3	46.6 ± 5	1.807	0.09[a]
	LG		46.3 ± 6.4	50 ± 6.7	4.097	0.001[b]
	MD	Pre	−0.8		0.372	0.7[a]
		Post	3.373		1.55	0.1[a]
Peroneal nerve amplitude (MV)	CG		1.6 ± 0.78	1.5 ± 0.8	1.910	0.07[a]
	LG		1.3 ± 0.7	1.7 ± 0.6	3.788	0.002[b]
	MD	Pre	−0.27		0.976	0.3[a]
		Post	0.316		1.240	0.2[a]
Sural nerve SCV (M/SEC)	CG		5 ± 9.1	4.5 ± 8	1.258	0.2[a]
	LG		5.1 ± 9.2	36.2 ± 12.4	10.234	0.0001[b]
	MD	Pre	0.133		0.0397	0.9[a]
		Post	31.813		8.355	0.0001[b]
Sural nerve amplitude (MV)	CG		1.6 ± 2.9	1.7 ± 3	1.835	0.08[a]
	LG		5.6 ± 10.1	26.1 ± 12.7	7.851	0.0001[b]
	MD	Pre	4.353		1.6111	0.1[a]
		Post	23.240		6.375	0.0001[b]

M ± SD, mean ± standard deviation; MD, mean difference; CG, control group; LG, laser group.
[a] Non-significant.
[b] Significant.

significant difference for sural nerve amplitude in favour of the laser group ($p = 0.0001$), see Fig 3.

Microcirculation results

Regarding skin blood perfusion, no statistically significant difference ($p > 0.05$) was found between the groups at pre-treatment measurement of heel, big toe and little toe, see Table 3. In the laser group, the microcirculation at the three points was increased significantly ($p = 0.001$) with no significant change in the control group, see Table 3; post-treatment measurement comparison between groups found a highly significant difference ($p = 0.001$) in favour of the laser group, see Fig. 4.

Pain level results

Both groups noted a decrease in mean pain scores after four weeks of treatment, see Table 3, with a statistically significant in favour of the laser group ($p = 0.0001$).

Discussion

From a pathophysiological standpoint, DPN is derived not only from injury to peripheral nerves, most commonly of microvascular origin [2,3], but repairing mechanisms are also defective including nerve growth factor and insulin-like growth factor [3]. So the treatment of DPN could be directed to improve microcirculation, enhance regeneration of nerve injury and reduce pain.

This study was designed to examine the effect of scanning He–Ne laser of wavelength 850 nm to treat patients with diabetic polyneuropathy. The outcome measurements are considered to be relief of pain, improvement of foot skin microcirculation, and to be measured objectively through electroneurography of peroneal and sural NCV and amplitude. Using VAS for pain assessment has some advantages in clinical trials as it is the most common and reliable type of pain scale [25]. In addition, its range and phraseology are known to be more reliable than those of other tests [29]. In electroneurography evaluation, sural SCV and peroneal MCV together serve as a simplified and effective diagnostic tool for diabetic polyneuropathy [30]. Peroneal nerve MCV correlates well with sural SCV, and sural nerve latency is often absent in patients with reduced peroneal MCV [31].

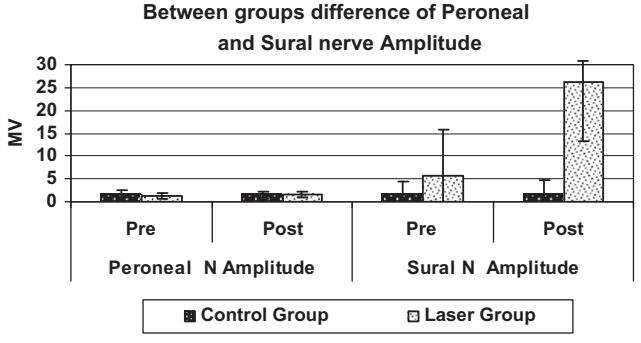

Fig. 3 Comparison of the pre- and post-treatment values (mean ± SD) of peroneal and sural nerve amplitude between the groups.

The study results showed that electrophysiological parameters (conduction velocity and amplitude) of peroneal motor nerve and sural sensory nerve and foot skin microcirculation were significantly increased in the laser group with no significant change in the control group. Also pain intensity level was significantly decreased in the laser group only. When comparing the post-treatment results of the groups, sural SCV and amplitude, foot skin microcirculation and pain intensity, had significant differences in favour of the laser group; there was no significant difference in either peroneal MCV or amplitude.

The improvement of electrophysiological parameters (peroneal MCV, amplitude & sural SCV, amplitude) in the Laser group could be explained as follows; laser has a biostimulational effect on the nervous system [16]. Earlier research findings suggest that LLL treatment appears to enhance reinnervation of target tissues subsequent to nerve injury [18–20]. Rochkind [17] 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 myelinization and axon regeneration [21,32]. An intriguing hypothesis would be that the improvement in cutaneous blood flow might be mirrored by a similar effect at the endoneural level, thus suggesting that an increment in nerve blood flow might be a mechanism through which laser induces improvement of peripheral nerve function. Carmeliet [33] demonstrated that blood vessels and nerves use similar signals and principles to differentiate, grow, and navigate towards their targets and, therefore, could also show synergistic responses to a common stimulus such as that induced by laser. Furthermore, the possible mechanism of the action of laser with respect to tissue regeneration and improved blood circulation were due to the following effects: (1) increased activity of some cells, such as leukocytes and phagocytes, and increased calcium in the cell cytoplasm; (2) interaction with cytochromes, stimulating redox activity in the cellular respiratory chain and resulting in cell activation [34,35], (3) accelerated cell division and growth; (4) activation of protein and cytokine synthesis; (5) stimulation of production of adenosine triphosphate (ATP), which enhances the cells' mitotic activity; and (6) relaxation of the vessel walls (vasodilatation) by photolysis of complexes such as nitric oxide [36,37].

The better response in sural sensory conduction study than in peroneal motor conduction study may indicate that (1) laser started its effects more peripherally in small nerve fibres that reflected on sural SCV and amplitude [9]; (2) sural SCV is measured through one site of stimulation and recording while peroneal MCV is measured through two sites of stimulation and recording that subtract the distal latency of peroneal nerve, which may reflect the peripheral laser effect [28] (this finding corresponds with the results obtained by Khullar et al. [32] who found actual function recovery in rats with compressed sciatic nerve without significant change in the evoked compound action potentials of the common peroneal nerve); (3) anatomically, the sural sensory nerve is a primary afferent neuron that is located superficially in the epidermis and dermis and was easily influenced by transcutaneous laser through both direct application to its branches on the plantar surface of foot and to its origin through lumbosacral application,

Table 3 Foot skin microcirculation and pain level values of the groups pre- and post-treatment.

Variables	Groups		Pre M ± SD	Post M ± SD	*t*	*p*-Value
Heel	CG		4.14 ± 1.63	4.19 ± 1.64	1.75	0.1[a]
	LG		4.51 ± 2.27	6.18 ± 1.95	4.2	0.001[b]
	MD	Pre	0.37		1.01	0.32[a]
		Post	1.99		4.4	0.001[b]
Big toe	CG		4.1 ± 1.81	4.19 ± 1.82	1.85	0.08[a]
	LG		3.97 ± 2.04	5.74 ± 1.77	9.99	0.001[b]
	MD	Pre	0.13		1.28	0.22[a]
		Post	1.55		9.79	0.001[b]
Little toe	CG		4.55 ± 2.8	4.73 ± 2.71	1.32	0.2[a]
	LG		4.5 ± 1.66	5.68 ± 1.38	7.2	0.001[b]
	MD	Pre	0.05		0.12	0.9[a]
		Post	0.95		2.2	0.04[b]
Pain level	CG		7.33 ± 0.61	6.93 ± 0.7	1.87	0.08[a]
	LG		7.2 ± 0.77	5.33 ± 0.97	7.29	0.001[b]
	MD	Pre	0.13		0.48	0.63[a]
		Post	1.6		5.23	0.001[b]

M ± SD, mean ± standard deviation; MD, mean difference; CG, control group; LG, laser group.
[a] Non-significant.
[b] Significant.

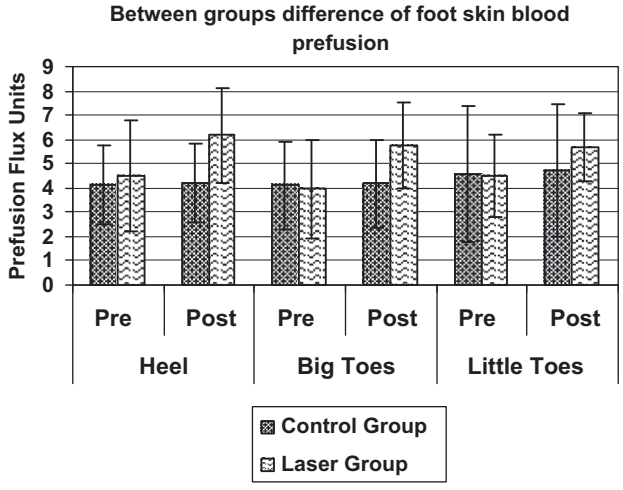

Fig. 4 Comparison of the pre- and post-treatment values (mean ± SD) of foot skin microcirculation between the groups.

while the peroneal is a deep motor nerve and the laser influenced it only indirectly through lumbosacral application. Parallel to the study's findings, statistically significant improvements were found in SCV, and sensory and motor distal latencies of median nerves in carpal tunnel syndrome treated by laser [38,39].

In addition, this finding is consistent with some results of Perić and Cvetkovic [10] who concluded that LILT had an indirect influence on the sensory axons function of the ulnar nerve (UN) in patients with painful DPN, where LILT significantly increases the neural potential amplitude of UN. But the study is inconsistent with the other Perić and Cvetkovic [10] results where LILT had no direct significant influence on SCV and MCV values of the peroneal nerve and the ulnar nerve of patients with DPN. The conflict between the two studies' results may be attributable to differences in the laser parameters and techniques used; our study used a scanning laser with wavelength 850 nm, while Perić and Cvetkovic [10] used a pointer laser with wavelength 904 nm. It has be mentioned that laser with wavelength 904 nm has no effect on the electrophysiological parameters of either sensory or motor function in normal and injured sciatic nerve [40,41]. In addition Perić and Cvetkovic [10] used laser with shorter duration.

Regarding to blood perfusion by laser application, the mean skin microvascular circulation measured at three different point of foot plantar surface was found to be increased by 35.8% in comparison with baseline. The degree of improvement achieved in the present study is comparable with that of previously published data [4,23] and with findings from studies dealing with the effects of other treatment modalities used to improve skin circulation in diabetic patients. This remarkable finding may suggest that, upon treatment with laser, the skin of individuals with diabetes generates a response at the microvascular level. The most likely explanation for triggering remote responses is the release of cytokines and growth factors into the circulation, which are responsible for systemic vasodilatation and formation of new capillaries [42,43]. Mack et al. [44] reported that low-intensity laser-induced release of the angiogenic cytokine was demonstrated to be the major component in wound fluid responsible for the induction of endothelial cell surface alkaline phosphatase, which dephosphorylates AMP to adenosine, a product of potent vasodilatory and anti-inflammatory activity.

Patients receiving LLLT had a 26.4% decrease of pain level through four weeks of treatment. Many authors had reported significant pain reduction with LLLT in acute and chronic painful conditions [45,46]. The exact mechanism whereby LLLT relieves pain is unknown. It may be due to increased ATP production by the mitochondria, and increased cellular oxygen consumption, increased serotonin and endorphins, anti-inflammatory effects and improved blood circulation in some cases [47]. There is also in vivo and in vitro studies evidence that 830 nm laser inhibits Aδ and C nerve fibre transmission [48],

given the etiology for the pain of diabetic neuropathy through abnormal activation of damaged nerve fibres, regenerating small-diameter nociceptive fibres may be involved. The perception of this pain is dependent on neurotransmission in the dorsal horn of the spinal cord [49]. Laser treatment would block the abnormal activity in the affected peripheral nerve or block neuro-transmission in the somatotopically related dorsal horn through application of laser on the corresponding segment of the spine (lumbosacral application). In addition transcutaneous or direct stimulation of sensory peripheral nerves (foot plantar surface application) is believed to produce analgesia through both of these mechanisms.

Conclusion

The study findings indicate that LLLT could be an effective therapeutic modality in the treatment of painful diabetic neuropathy in that it is able to modify pain, foot skin microcirculation and some electrophysiological parameters of peripheral nerve function.

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