Original article

EFFECTS OF MLS-LASER ON NEUROPATHIC PAIN IN DIABETIC SENSOMOTOR NEUROPATHY

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ABSTRACT:
About 20-50 % of patients with diabetes and about 60 % of those with diabetic neuropathy develop neuropathic pain, which is characterized by tingling, burning, sharp, shooting, or stabbing sensations, and even electric shock-like sensations. Painful diabetic neuropathy can significantly affect the quality of life of patients with diabetes, the ability to perform daily activities and negatively affect mood. According to the 2021 consensus of an international panel of experts regarding the treatment of painful distal symmetric polyneuropathy, non-pharmacological forms of treatment should also be considered due to unsatisfactory pharmacotherapy. A number of studies have demonstrated the role of photobiomodulation as a non-pharmacological method of treating painful diabetic neuropathy.

The purpose of this placebo-controlled, longitudinal study was to investigate the effect of high-energy MLS-laser therapy on neuropathic pain.

Material and methods: A total of 69 cases of patients with type 2 diabetes and painful diabetic neuropathy of the lower extremities were followed, divided into two groups: an experimental - 41 patients received high-energy laser radiation and a control (placebo) group - 28 patients, with a "mock" laser treatment. For objectification of pain, the Bulgarian version of the short form of the McGill pain questionnaire, version SF-MPQ-2, which includes the visual analog scale (VAS), was used. Comparisons between groups were performed with parametric or non parametric tests depending on the distribution of the variables, the number of the compared groups and the study pre test – post test design.

Results: The pain index, reported by the McGill questionnaire, in the experimental group, decreased by - 63.2 % at the end of the nine-day treatment and by - 56.1 % at the 90th day after the start of treatment compared to the value before therapy. In the control group, there was a minimal change at the end of treatment (day 21), which did not persist until the end of the observation period (day 90).

Conclusions: MLS laser therapy significantly increases the pain threshold and should be considered a safe, non-pharmacological adjunct to standard therapy in patients with painful diabetic peripheral neuropathy.

Keywords: MLS-laser, neuropathic pain, McGill Pain Questionnaire, diabetic neuropathy,

INTRODUCTION

According to the International Association for the Study of Pain (IASP), neuropathic pain is defined as "pain caused by a lesion or disease of the somatosensory nervous system." Painful diabetic neuropathy is a common subtype of peripheral neuropathy and is defined as "pain that is a direct consequence of abnormalities in the peripheral somatosensory system in people with diabetes" [1].

Although pain is one of the main symptoms of diabetic neuropathy, its pathophysiological mechanisms are still not fully understood. The toxic effect of hyperglycemia plays an important role in the development of this complication. Various theories attempt to explain the cause of painful diabetic neuropathy, such as changes in blood vessels feeding peripheral nerves, metabolic and autoimmune disorders. Other hypotheses suggest glial cell activation in the spinal cord, changes in sodium and calcium channel expression, and more central pain mechanisms, such as increased thalamic vascularity and disbalance of facilitatory and inhibitory descending pathways [2]. There are studies that found that peripheral perfusion is reduced not only in the nervous tissue but also in the skin, which is important physiological evidence of a change in microvascular circulation [3].

About 20-50 % of patients with diabetes and about 60 % of those with diabetic neuropathy develop neuropathic pain [1]. There is still no clear hypothesis to explain why some patients develop the painful form of the disease while others do not. What is of interest is that the intensity of pain is usually not related to the severity of the neuropathy and can occur even in the absence of nerve damage [4].

Advanced age, long history of diabetes, alcohol use, and smoking are risk factors associated with neuropathic pain in diabetes.

Diabetic neuropathic pain is characterized by tingling, burning, sharp, shooting, or stabbing sensations, and even electric shock-like sensations. It is usually moderate to severe and often worsens at night, disrupting sleep. The pain can be constant and accompanied by cutaneous allodynia, which can significantly affect the patient's quality of life, the ability to perform daily activities and negatively affect mood. It can also be a reason to withdraw from

recreational and social activities and be associated with depression [5].

Improving glycemic control and lifestyle changes are used to prevent painful peripheral neuropathy, and a few medications are used to relieve pain. Antidepressants are recommended as first-line therapy, including tricyclic antidepressants (amitriptyline and nortriptyline), reversible serotonin and norepinephrine reuptake inhibitors (duloxetine and venlafaxine), and gabapentinoids (gabapentin and pregabalin).

According to the 2021 consensus of an international panel of experts regarding the treatment of painful distal symmetric polyneuropathy, non-pharmacological forms of treatment, such as transcutaneous electrical nerve and muscle stimulation and acupuncture, should also be considered due to unsatisfactory pharmacotherapy. Spinal cord stimulation is recommended for patients with refractory, painful diabetic sensomotor polyneuropathy who have exhausted all other treatment options [6].

Several studies prove the role of another non-pharmacological method of treatment, such as photobiomodulation, involving laser treatment. The product of scientific research aimed at overcoming the limitations of traditional laser therapy is the multi-wave fixed system – MLS (Multiwave Locked System), combining two wavelengths, created by an Italian company.

A basic principle in treatment with lasers with the simultaneous application of two or more wavelengths is the principle of synergism. It achieves unidirectionality of the used components of the complex, i.e. strengthening the positive healing effect and prolonging the remission time [7].

It is suggested that the improvement of skin blood circulation has a mirror effect at the endoneurial level. Blood vessels and nerves use similar principles and signals for differentiation and growth, so it follows that they can show a synergistic response to a common stimulus, including the laser. An increase in nerve blood flow is a mechanism by which the laser improves peripheral nerve function [8].

The aim of this prospective, single-blind, placebo-controlled, longitudinal study was to investigate the effect of high-energy MLS-laser therapy on neuropathic pain.

MATERIALS AND METHODS:

A total of 69 cases of patients with type 2 diabetes and painful diabetic neuropathy of the lower extremities were followed. Patients were randomly divided into two groups: an experimental and a control (placebo) group. The experimental group included 41 patients who received high-energy laser radiation. The control (placebo) group included 28 patients who received "sham" laser treatment by directing the robotic device and light guide without releasing the beam.

The criteria for inclusion in the study were: age over 18 years, duration of diabetes no more than 15 years, discontinued intake of symptomatic therapy for neuropathic pain for 24 hours before inclusion in the study, no application of a course of physical therapy in the last six months, Fitzpatrick skin type I to IV, signed informed consent statement.

The exclusion criteria were: age under 18 years, comorbidity forming contraindications for laser treatment (systemic neoplastic, infectious, autoimmune diseases), hemorrhages, familial polyneuropathy, pregnancy, chronic alcohol abuse, skin type - V and VI types according to Fitzpatrick, inability to understand and follow study instructions, refusal to sign informed consent regarding therapeutic procedures, unwillingness to participate in treatment for personal reasons.

For objectification of pain, the Bulgarian version of the short form of the McGill pain questionnaire, version SF-MPQ-2, was used. In 2009, a revision was conducted by Dworkin et al. on the short form of the McGill Pain Questionnaire1 (SF-MPQ). This revision involved the inclusion of seven symptoms specifically associated with neuropathic pain, as well as the replacement of the original four-point rating scale with a 0-10 scale for all 22 items. These modifications aimed to enhance the quality of responses obtained from participants. This research aimed to assess the reliability, validity, and structure of the SF-MPQ (SF-MPQ-2) in a sample of 882 persons diagnosed with diverse chronic pain syndromes, as well as in a subgroup of 226 patients specifically diagnosed with severe diabetic peripheral neuropathy. The observed results justify considering a variant of the SF-MPQ-2 as a dependable instrument for utilisation in clinical research [9]. The minimum score for pain that can be obtained as a final score is 0, and the maximum is 10. Patients completed the McGill Pain Questionnaire (SF-MPQ-2) three times: before the start of treatment, after completion of the therapeutic course (on the 21st day) and on the 90th day from the start of therapy.

We used an MLS laser, M6 of ASA Laser, Italy. It is a class IV NIR diode laser, distinguished by combining and synchronizing two emissions with different wavelengths - ë-808 nm in constant mode and a second laser diode with ë-905 nm in pulsed mode.

The treatment was carried out by a regimen of single application per day, every other day. The treatment course was a total of 9 procedural days, three procedures per week, three weeks. The therapeutic methodology used was carried out in two stages. First, a scan of the foot (100-175 cm²) of both lower extremities (fig. 1) was performed 20 cm away from the skin with an MLS fixed, robotic multi-diode device (remote technique). Then, 7 areas on each lower extremity (fibular neck area, popliteal fossa, medial and lateral malleolus, mid-gluteal fold, and two on the dorsum of the foot) were treated, each 3.14 cm² in area, with the MLS single-diode handheld applicator (contact methodology), with a total area of 21.98 cm² (fig. 2). The frequency used in both stages is 1500 Hz, Int. 100 %, energy density: 2.52 J/cm2 in the remote method and 6.04 J/cm2 in the contact method.

Statistcial methods

Quanitative variables are presented as absolute values and percentages and quantitative variables as mean and SD, or median values and IQR, dependeing on their distribution. The type of the distribution of the variables was assessed with Kolmogorov – Smirnov test. The test for differ-

ences in the baseline characteristics of the two study groups, was performed with either a t-test, Mann-Whitney test or chi-square test, as appropriate. To determine whether the treatment was effective, we compared the study's outcomes before and after intervention for the experimental and the control groups using Wilcoxon signed rank test, or ANOVA in pre-test-post-test design. Comparissons of the effects between the experimental and control groups were performed with Kruskal-Wallis or ANOVA tests. Differences were considered significant at alpha level <0.05. Anlysis were performed with IBM SPSS 26.0 (Chicago, IL, USA).

Fig. 1. Foot scan

Fig. 2. Areas treated with a single diode hand applicator.

RESULTS

Prior to the beginning of the treatment, there existed no statistically significant disparity between the experimental and control groups with respect to the duration of diabetes and neuropathy, demographic and anthropometric indicators, the therapeutic interventions used to treat diabetes, as well as the levels of glycated haemoglobin. (Table 1).

Table 1. Comparison between experimental and control group by main observed characteristics.

	Experimental group	Control group	
Number of participants	41	28	p
Males, n (%)	21 (51.2)	15 (53.6)	0.848
Age	61 (55-68.5)	61.5 (54.3-72.0)	0.957
Height	169 (165-176)	169.5 (163.0-175.8)	0.884
Weight	90 (73.5-100.0)	89 (73.3-100.0)	0.739
Duration of diabetes	10 (7.0-13.5)	10.5 (7.2-15.0)	0.512
Duration of neuropathy	5 (2.5-7.0)	7 (3.0 -8.8)	0.586
HbAl c before	7 (6.2-7.95)	6.95 (6.1-8.0)	0.811
HbAl c 90th day	7 (6.2-8.00)	7.1 (6.1-8.0)	0.884
Insulin therapy	9 (22.0)	4 (14.3)	0.424

Prior to the treatment, the observed and compared groups exhibited perfect comparability with respect to the subjective variables under consideration (Table 2). All participants (100 %) from both groups reported experiencing pain of varying characteristics. The most frequently mentioned qualities of pain in the experimental group were "cramping" by 63 % of patients, "aching pain" by 56 % and again 56 % "tingling "or "pins and needles". In the control group, 75 % reported "tingling "or "pins and needles", 75 % "aching pain", and 72 % "stabbing" pain.

Table 2. Comparison between experimental and control group on subjectively assessed indicators before the intervention

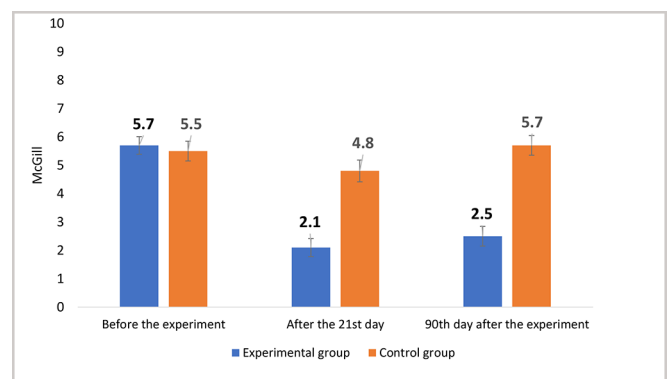|	Experimental group	Control group	
Number of participants	41	28	p
Sensation of paresthesias			
with perestesias	29 (70.7)	23 (82.1)	0.28
without perestesias	12 (29.3)	5 (17.9)	
Sensations of cramping			
with cramps	18 (43.9)	9 (32.1)	0.326
without cramps	23 (56.1)	19 (67.9)	
Sensibility			
abnormal	18 (43.9)	16 (57.1)	0.28
normal	23 (56.1)	12 (42.9)	
Pruritus			
report	11 (26.8)	6 (21.4)	0.609
doesn't report	30 (73.2)	22 (78.6)	
Presence of pain	41 (100.0)	28 (100.0)	

Upon comparing the groups prior to treatment, it was observed that there was no statistically significant difference in the pain index values (McGill: Experimenal: 5.7±1.92 and Control: 5.5±1.84). However, subsequent to the therapy (on the 21st day) and on the 90th day thereafter, a statistically significant difference was observed between the two groups. (Fig.3).

The observed change in the indicator's value following the treatment in the control group exhibited a modest reduction in pain sensation, with an average value of 4.8±2.03. In contrast, the experimental group experienced a more substantial decrease, with an average value of 2.1±2.05. The difference between the two groups was statistically significant. (p<0.001).

The control group exhibited a significant rise (5.7±1.83) in the pain index value on the 90th day post-treatment, as compared to both the value observed on the 21st day and the baseline value before to treatment. In the experimental group, there was a statistically significant rise (mean ± standard deviation: 2.5 ± 2.23) found when compared to the 21st day. However, this increase did not reach the pre-treatment value.

The dynamics of the change in the values of the pain index in the experimental group, reported by the short form of the McGill questionnaire, was to decrease at the end of the treatment, demonstrating the immediate effect, as well as on the 90th day, reflecting the long-term effect

Fig. 3. Comparative performance of the pain index between the experimental and control groups as measured by the McGill Pain Questionnaire

of the therapy. In the control group, there was a minimal change at the end of treatment (day 21), which did not persist until the end of the observation period (day 90).

The experimental group experienced a drop in pain index values as measured by the short form of the McGill questionnaire. This decrease was observed both immediately after the treatment and on the 90th day, indicating both short-term and long-term effects of the therapy. The control group exhibited a negligible alteration at the end of the treatment phase (day 21), which was not sustained until the conclusion of the observation period (day 90).

DISCUSSION:

The control group exhibited a pain index reduction of -12.7 % following the nine-day treatment regimen. In contrast, the experimental group saw a significantly greater reduction of -63.2 %. This difference between the groups was statistically significant, with a p-value of less than 0.001 (p< 0.001). The observed decrease in pain, although not statistically significant in the control group, could perhaps be related to the psychological impact of more interactions with the research physician between the initial assessment and day 21. The patient's condition evokes a sense of concern, which in turn generates an anticipation of amelioration.

On the 90th day following treatment, the control group exhibited a pain index rise of 3.7 % compared to the baseline measurement, and an 18.8 % increase compared to the measurement taken on day 21. The experimental group exhibited a significant 19 % rise compared to day 21; nonetheless, the indicator did not revert to its initial values. There exists a statistically significant difference in comparison to the initial state, with a value of 56.1 % relative to the pre-treatment condition.

One potential mechanism underlying the nociceptive impact of laser treatment involves the release of cytokines and growth factors into the bloodstream. These substances are responsible for the vasodilatation of blood vessels and the development of new capillaries. Additionally, laser treatment may enhance ATP production by mitochondria and increase cellular oxygen consumption, thereby promoting nerve regeneration [10]. Another potential factor is the reduction in serum concentrations of MCP-1, IL-6, RANTES, TNF-α, IL-6, PGE2, COX-2, as well as the decrease or inactivation of NF-κB [11]. The pain-relieving effect has been attributed by some authors to an elevation in the nociceptive threshold, which inhibits the transmission along A and C fibres [12], as well as the release of endorphins. The induction of analgesia through transcutaneous or direct stimulation of peripheral sensory nerves involves the application of a laser to the plantar surface of the foot. This stimulation effectively blocks neurotransmission along A-δ and C-fibers to the posterior horn of the spinal cord. Additionally, it activates the damaged small fibre nerves [13].

CONCLUSION:

In summary, the data acquired from this longitudinal study, which employed a placebo-controlled design, provide evidence of the potential efficacy of MLS laser therapy. The application of a high-power NIR laser that combines two distinct wavelengths (808 nm and 905 nm) yielded a statistically significant amplification in the pain threshold.

Considering the non-invasive characteristics of the intervention and its notable safety performance (absence of any known adverse local or general reactions), it is reasonable to regard deep tissue laser therapy as a secure and non-pharmacological complement to standard therapy for individuals suffering from painful diabetic peripheral neuropathy.

Abbreviations:
MLS - Multiwave Locked System

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