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Effects of electrotherapy in neuropathic pain management in patients with diabetic peripheral neuropathy: A narrative review

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Abstract
Diabetes is one of the most prevalent diseases worldwide and Diabetic Peripheral Neuropathy (DPN) is the most common neuropathic syndrome affecting approximately 50% of patients with type 2 diabetes. One of its main clinical manifestations is neuropathic pain, which significantly complicates the daily life of patients and leads to a low quality of life related to health. The aim of this review is to describe research data on the means of electrotherapy used and their effects in the treatment of pain in patients with DPN. The PubMed, PEDro, Scopus and Google Scholar databases were searched in English with the following keywords: Diabetic Painful Neuropathy, Low-level Laser Therapy, Transcutaneous Electrical Nerve Stimulation, and Electromagnetic Fields. The review included 10 clinical studies published in the period of 2004-2019. Discussion-Conclusions: Low-power lasers, pulsed electromagnetic fields and Transcutaneous Electrical Nerve Stimulation (TENS) are treatment options for treating neuropathic pain in patients with DPN and are considered safe, effective, with minimal side effects compared to medication. However, diabetic neuropathic pain remains a challenge for health scientists. Although there is scientific evidence for the contribution of electrotherapy to its treatment, more focused research is needed.

Keywords: Diabetic neuropathy, low-level laser therapy, transcutaneous electrical nerve stimulation, electromagnetic fields

Introduction
Diabetes is one of the most prevalent diseases in the world. In 2018, approximately 350 million people suffered from diabetes, including nine out of 10 people with diabetes mellitus (DM) [1]. The global prevalence of DM will reach approximately 629 million patients by 2045. Neuropathic syndromes are common complications of DM, with a prevalence of 66% in type 2 DM (DMT2) and 59% in type 1 DM (DMT1). The most common neuropathic syndrome is Diabetic Peripheral Symmetric Polyneuropathy (DPSP), which occurs in approximately 50% of patients with DM [2].
DPSP is defined as symmetrical, length-dependent (small diameter nerve fibers are most affected) sensory polyneuropathy. Symptoms are located in the lower limbs, mainly on the soles of the feet and toes, with the main clinical manifestations being sensitivity to injury and leg ulcers and neuropathic pain, which occurs in about 1/5 of patients. This pain is characterized as intense and severe, caustic, "like an electric shock" and is associated with sleep disorders due to worsening at night [2]. These symptoms affect the social and economic well-being [3] and mental health of patients, with major manifestations of depression and anxiety [4].
Diabetic Peripheral Neuropathy (DPN) needs interdisciplinary management, which mainly aims at optimal glycemic control, lifestyle modification with diet and exercise, management of vascular risk factors [2], good foot care and pain management [5]. Neuropathic pain is often persistent and is associated with low patient satisfaction with treatment, making treatment extremely difficult for health scientists [3]. Medication helps manage pain, but many patients do not respond well to it and may also experience side effects that aggravate their overall condition. Thus, alternative therapeutic methods are sought for the management of diabetic neuropathic pain, such as therapeutic exercise [6, 7] and electrotherapy [8, 9].

The use of low-power lasers is common in the care of diabetic foot, as it helps to heal ulcers and improve microcirculation. Various studies have reported that low-power lasers also promote nerve regeneration and reduce neuropathic pain [1]. Transcutaneous Electrical Nerve Stimulation (TENS) is used to manage painful conditions and has been studied in the treatment of neuropathic pain and in patients with DPN [8]. Electromagnetic fields also have analgesic, anti-inflammatory, anti-swelling action and cause vasodilation. They are considered a safe complementary treatment for patients with DPN, however, their application is more limited [10].

The aim of this review is to present research data on the aforementioned electrotherapy tools and their results in the treatment of pain in patients with DPN.

Literature review

The PubMed, PEDro, Scopus and Google Scholar databases were searched in English with the following keywords: Diabetic Painful Neuropathy, Low-level Laser Therapy, Transcutaneous Electrical Nerve Stimulation, and Electromagnetic Fields. The review included 10 clinical studies published in the period of 2004-2019. The following are the main conclusions of the included articles:

Zinman *et al*. [11] studied the application of low power laser in 50 patients over 18 years, with DMT2 and painful DPN lasting more than three months. All patients received placebo laser therapy for the first two weeks of the study and then were equally divided into placebo and laser groups, receiving two weekly sessions for four weeks. The laser group used a device with a wavelength of 905nm and an average power of 0-60mW on the dorsal and plantar surface of the feet for five minutes. There was a reduction in pain with placebo treatment for the first two weeks. After four weeks of intervention, the laser group had an additional reduction in pain compared to the placebo group. The results, however, do not provide sufficient evidence to suggest this laser treatment.

Furthermore, Yamany and Sayed [12] studied the effect of low-power laser treatment in patients aged 45-60 years, with DMT2 and with painful DPN lasting more than six months. In the treatment group (15 patients), a continuous emission laser device He-Ne was used, with a wavelength of 850nm and dosage of 5.7 J/cm² in the lower back (O2-I1) and the plantar surface of the foot for 15 minutes per area per session, three times per week for four weeks. The control group (15 patients) received placebo laser treatment. Pain was significantly reduced, potential amplitude, gastrocnemius nerve conduction velocity, and foot skin microcirculation were significantly improved in the treatment group compared to the control group.

The results of low power laser treatment were also the study focus of Shashi Kumar *et al*. [13] in 19 patients with a mean age of 50 years, with DMT2 and painful DPN lasting an average of eight years. Application was performed by scanning, with dosage of 3.1J/cm² and wavelength of 632.8nm to the plantar and dorsal surface of the foot for nine minutes. Additionally, a probe was applied (dosage 3.4J/cm², wavelength 660nm and 850nm and density 50-150mW/cm²) in the iliac fossa and the fibular neck. The treatment lasted 10 days. The analysis of the results showed a significant reduction in pain, an improvement in the microcirculation in the feet, and a significant reduction in the lower limit of vibration perception.

In another study, Wróbel *et al*. [14] investigated the effects of low-frequency pulsed electromagnetic fields on pain intensity, quality of life, sleep and glycemic control in 32 patients (intervention group) with DMT1 or DMT2 and painful DPN lasting 23 months. The other 29 patients (control group) involved in the study received placebo treatment. The treatments lasted three weeks, 20 minutes per day, five days per week. The magnetic fields had a frequency of 180-195Hz, a power of 100μT and an intensity of 130v/m. There was a reduction in pain and similar improvements in the other variables without significant differences between groups. Electromagnetic field therapy was shown to improve pain relief, quality of life, sleep disorders and glycemic control, but held no significant advantage over placebo.

Further on electromagnetic fields, Graak *et al*. [15] compared the effect of two low-power and low-frequency pulsed electromagnetic fields with medication on pain and nerve conduction in 30 patients aged 40-68 years with DMT2 and painful DPN. Patients were randomly divided into three equal groups. In the first and second groups, low-power electromagnetic fields (frequency of 600 and 800Hz respectively) were used for 30 minutes per day for 12 consecutive days. The third group received the usual medication. Significant reduction in pain, reduction in latency and increase in peroneal nerve conduction velocity were observed in the first and second groups compared to the third. It was concluded that pulsed electromagnetic fields can be used complementary to reduce pain and to slow the progression of neuropathy.

Moreover, Battecha [16] studied the effect of pulsed electromagnetic fields in 15 patients (intervention group) aged 40-50 years with DMT2 and painful DPN lasting 10 years. The intervention group received therapy with fields of 50Hz frequency and 20G intensity for 20 minutes in combination with a physiotherapy program (exercises of proprioception, balance and range of motion), three times per week for four weeks. The control group (15 patients) followed only the physiotherapy program, three times per week for four weeks. There was a significant reduction in pain intensity and a significant improvement in the peroneal nerve conduction velocity in both groups, with better results coming from the combination of electromagnetic fields and physiotherapy.

Regarding other electrical therapies, Bulut *et al*. [17] compared the efficacy of TENS versus placebo TENS in patients with a mean age of 59 years with DMT1 or DMT2 and painful DPN. Group A consisted of 20 patients that received TENS treatment at a frequency of 80 HZ in the lower back, after discontinuing medication for neuropathic pain 48 hours before each treatment. Group B consisted of 20 patients that received placebo TENS treatment. The treatments were applied for 30 minutes daily for 20 days in both groups. The reduction in pain at the end of the program was greater for group A. TENS appeared to be an effective and safe treatment option and the effect of placebo TENS was limited.

Further on the subject of TENS, Serry *et al*. [18] compared therapeutic intervention with TENS versus aerobic exercise and medication in patients aged 45-60 years with DMT2 and painful DPN of at least 5 years. The first group of 20 patients received TENS treatment with a portable dual channel device (one for each lower limb) with a frequency of 14Hz, pulse time 250μs, 30 minutes per session, three

times per week for eight weeks. The second group of 20 patients followed an aerobic exercise program on a stationary bike, for 40 minutes per session, three times per week for eight weeks. The third group of 20 patients received standard medication. Pain reduction was more significant in the TENS group. Neither TENS nor aerobic exercise improved intraplantar nerve conduction velocity, initially evaluated.

Upton *et al*. [19] studied the efficacy of conventional TENS (80Hz, 200μs) versus low-frequency electro acupuncture (2Hz, 200μs) in pain relief in five patients, 61-88 years, with DMT2 and painful DPN lasting more than six months. Patients received the two forms of TENS treatment with a seven-day break between them and were randomly distributed without knowing the original form. The TENS were placed laterally on the lower back, for 30 minutes daily for 10 days. Significant pain relief was observed during one or both treatments and it was maintained for 1-2 hours after.

Lastly, Zakerkish *et al*. [20] investigated the efficacy of nortriptyline against TENS in patients with a mean age of 55 years with DMT1 or DMT2 and painful DPN. The first group of 20 patients received TENS treatment (4Hz, 200μs, in the course of the peroneal nerve) for 18 sessions of 30 minutes for six weeks. The second group of 19 patients were treated with nortriptyline (25 to 75mg, once per day) for six weeks. There was a reduction in pain in both groups, but more significant for patients receiving nortriptyline. In numbers, 50% pain relief compared with the initial score was observed in 14 patients (73%) in the nortriptyline group and in six patients (30%) in the TENS group. Side effects occurred in 15% of patients in the TENS group (cramps) and in 55% of patients in the nortriptyline group (drowsiness).

Discussion-Conclusions

Three electrotherapy tools related to the management of neuropathic pain in patients with DPN are presented in this paper. In summary, based on the studies included, the benefits of electrotherapy may include the following:

Three studies have studied the effect of low-power laser treatment in patients with chronic painful DPN [11-13]. Two of these studies showed positive results in reducing pain and increasing skin microcirculation in the feet. One study also found a reduction in the lower vibration perception threshold [13] and another noted an increase in the potential amplitude and conduction velocity of the gastrocnemius nerve [12].

Three studies evaluated the effects of low-frequency pulsed electromagnetic fields [14, 16]. Electromagnetic fields had better results in reducing pain compared to medication, with the added benefit of reducing latency and increasing peroneal nerve conduction velocity. The addition of electromagnetic fields to a physiotherapy program was shown to help better treat pain and increase the rate of peroneal nerve conduction.

Four studies have investigated the effect of TENS and all have shown a significant reduction in neuropathic pain [17-20]. One study found that applying TENS with a frequency of 14Hz and a pulse time of 250μs for 30 minutes, 3 times a week is a more effective treatment for pain relief than aerobic exercise [18]. In another study, nortriptyline was found to be more effective in pain management, but a higher percentage of patients experienced side effects [20]. Only one small-sample pilot study reported maintenance of pain relief for 1-2 hours after TENS treatment [19].

The application of low-power lasers, pulsed electromagnetic fields and TENS in patients with painful DPN seems safe, effective and with minimal side effects. Diabetic neuropathic pain is a challenge for health scientists and although more focused research is needed, there is scientific evidence for the contribution of electrotherapy to its treatment.

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