

Nonpharmacologic therapies in diabetic neuropathic pain: a review

Terapias não farmacológicas no alívio da dor neuropática diabética: uma revisão bibliográfica

Terapias no farmacológicas en el alivio del dolor neuropático diabético: una revisión bibliográfica

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ABSTRACT

Painful diabetic neuropathy is characterized by intense pain. The objective was to conduct a literature review regarding the pharmacologic therapies used to relieve that pain. A literature search was conducted of six (6) data sources, in the last 12 years (1998 to 2010) using the keywords: *diabetes, diabetes, painful neuropathy, neuropathic pain, treatment*, and other similar terms. Thirteen articles were selected that addressed the use of acupuncture, reiki, photic stimulation, electromagnetic stimulation of neural electrical stimulation, laser therapy. The non-pharmacological therapies are being used to alleviate diabetic neuropathic pain, however, there is no consensus about the effectiveness of such treatment in reducing this pain. The knowledge base on the subject is scarce, especially in Brazil.

Keywords: Diabetic neuropathies; Diabetes mellitus; Pain; Therapeutics

RESUMO

A neuropatia diabética dolorosa caracteriza-se pela dor de difícil controle. O objetivo do estudo foi analisar a produção bibliográfica a respeito das terapias não farmacológicas utilizadas no alívio dessa dor. Pesquisa bibliográfica, por meio de seis (6) fontes de dados, nos últimos 12 anos (1998 a 2010), utilizando os descritores diabetes, diabetes mellitus, neuropatia dolorosa, dor neuropática, tratamento e similares. Foram selecionados 13 artigos, que abordaram o uso de acupuntura, reike, fotoestimulação, estimulação eletromagnética neural, estimulação elétrica, terapia a laser. As terapias não farmacológicas estão sendo utilizadas com o propósito de aliviar a dor neuropática diabética, no entanto, ainda não há consenso sobre a eficiência desse tipo de tratamento na redução dessa dor. A produção de conhecimento sobre a temática é escassa, especialmente, no Brasil.

Descritores: Neuropatias diabéticas; Diabetes mellitus; Dor; Terapêutica

RESUMEN

La neuropatía diabética dolorosa se caracteriza por el dolor de difícil control. El objetivo del estudio fue analizar la producción bibliográfica respecto a las terapias no farmacológicas utilizadas en el alivio de ese dolor. Se trata de una investigación bibliográfica, por medio de seis (6) fuentes de datos, en los últimos 12 años (1998 a 2010), utilizando los descriptores diabetes, diabetes mellitus, neuropatía dolorosa, dolor neuropático, tratamiento y similares. Fueron seleccionados 13 artículos, que abordaron el uso de acupuntura, reike, fotoestimulación, estimulación electromagnética neural, estimulación eléctrica, terapia con laser. Las terapias no farmacológicas están siendo utilizadas con el propósito de aliviar el dolor neuropático diabético, mientras tanto, aun no hay consenso sobre la eficiencia de ese tipo de tratamiento en la reducción de ese dolor. La producción de conocimiento sobre la temática es escasa, especialmente, en el Brasil.

Descriptores: Neuropatías diabéticas; Diabetes mellitus; Dolor; Terapêutica

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INTRODUCTION

Painful diabetic neuropathy (PDN) is a complication of diabetes *mellitus*, characterized by the somatic and/or autonomic nerves degeneration and can affect any nerve in the human body⁽¹⁾. It is estimated that over 50% of diabetics develop neuropathy after 25 years of disease⁽²⁾, and although such complication is only subclinical, in almost 100% of cases, there are electrophysiological indications of neuropathy alterations⁽³⁾. Moreover, 10% of people with type 1 diabetes, and 20% of type 2 present severe pain⁽³⁻⁴⁾.

The diabetic neuropathy pain presents moderate-severe intensity⁽⁴⁻⁵⁾ and is described as tingling, burning, continuously sore, searing, with a stinging sensation, located distal, bilateral and symmetrically, with abnormal sensory changes, such as allodynia or hyperalgesia^(4,6).

Pain treatment is complex: several anti-nervous drugs, such as tricyclic antidepressants, anticonvulsants, topical agents, and sympathomimetics have been used, seeking improvements in nerve function and blocking the transmission of pain impulses, however, results are still dissatisfactory^(7,9). Moreover, the adverse effects of different drugs motivate the search for new approaches that might assist in the appropriate management of pain in this population, since this experience directly affects the quality of life, often leading to disability⁽¹⁰⁻¹¹⁾.

Accordingly, non-pharmacological therapies such as acupuncture, light therapy with infrared monochrome laser therapy of low intensity, percutaneous electrical nerve transmission, reiki, and electromagnetic stimulation (FREMS) have been used⁽¹²⁻¹⁹⁾. However, there is no consensus on the use of these therapies, as effective remedy for the treatment of PDN.

Considering the above mentioned, it is relevant to highlight the importance of studies on the management of diabetic neuropathic pain, in order to prevent unnecessary suffering and reduce direct and indirect costs to the individual, family and healthcare services. Furthermore, knowing and producing knowledge about non-pharmacological Therapies for Pain Relief can contribute to building a knowledge base for nursing and healthcare professionals and being more autonomous in solving problems arising from painful experiences. This study was proposed, aiming to contribute to the knowledge construction in the area and aims to analyze the bibliographic production on non-pharmacological treatments for diabetic neuropathy pain.

METHODS

The literature review was performed with a scope on publications from the past 12 years (1998-2010), on non-pharmacological therapeutic analgesics used for pain relief

in the PDN. The bibliographic sources investigated were: Literatura Latino-Americana e do Caribe em Ciências da Saúde – LILACS (Latin-American and Caribbean Literature on Health Sciences), MEDLINE (International Literature on Health Sciences), SCIELO (Scientific Electronic Library Online), Cochrane and Biblioteca Digital de Teses e Dissertações da Universidade de São Paulo – USP (Cochrane and Digital Library of Theses and Dissertations of USP); and the following subject descriptors: diabetes, diabetes mellitus, neuropatia dolorosa, dor neuropática, tratamento, pain, neuropathy, neuropathic pain, painful diabetic neuropathy.

Initially, 189 studies were identified. In the first analysis, articles found in more than one information source, duplicated articles and those dealing with pharmacological therapy were excluded, resulting in 21 articles. After the second analysis, 13 studies were selected; those which met the inclusion criteria established by the authors for the present review, namely primary publications, in Portuguese, English or Spanish, which were available online in full.

Articles were found through data searches in the Virtual Health Library (VHL), Capes Journals Portal and Google. National Library services were not used.

Selected articles were assessed through analytical reading, and data on the journal (title, language, publication date) and the study (design, results, limitations) were recorded on a standardized instrument. Further on, data were organized through the program “Microsoft Word”. The present research authors discussed doubts regarding the data, seeking agreement on the inclusion of studies in the review.

RESULTS

The predominant study type included the double blind, randomized, and placebo-controlled approaches, and therapeutic modalities included acupuncture^(17,20), reiki, electrical stimulation⁽²²⁾, frequency rhythmic electrical modulation system (FREMS)^(12,23), pulsed electromagnetic fields (PEMF)⁽²⁴⁾, the low intensity laser, monochromatic infrared^(15,25-26), and percutaneous electrical stimulation (PENS)⁽²⁷⁾.

DISCUSSION

Among non-pharmacological therapies used with the purpose of relieving pain in people with diabetic neuropathy, acupuncture was mentioned in two of the selected studies. In one of them⁽¹⁷⁾, a randomized and controlled study, two types of acupuncture were utilized - Traditional Chinese Medicine (TCM) and Japanese acupuncture, in a sample of seven (7) individuals with PDN, over 18 years old, with pain scores greater than

four (4) in the VAS scale (0-10). Three people received TCM and four, Japanese acupuncture. Each group had ten sessions of each type, one per week. Clinically, individuals who received Japanese acupuncture reported a greater reduction in daily pain scores, not maintained over time; nevertheless, there was no significant difference in pain reduction when using both modalities. In a second study⁽²⁰⁾, Chinese acupuncture was used to treat 44 people with PDN, 32 males, with an average of 57.2 years old and an average disease existence of 13.2 years. Participants received six applications of acupuncture in both legs for 10 weeks. The results showed that although 77% of participants reported improved symptoms, only 21% achieved complete relief.

Authors^(17,20) highlighted the fact that when acupuncture is used responsibly, therapy can be an option for those who do not respond or suffer adverse effects from the drugs used for pain relief. They also emphasize the need for randomized, double-blind, placebo controlled studies, pointing to the difficulties to this type of research: ethical-related issues, difficulties in maintaining blinded professionals and patients, given the characteristics of acupuncture and the use of sham (incorrect acupuncture), which always cause some type of sensory afferent stimulation when needles are inserted in the body.

The percutaneous electrical nerve stimulation (electrical stimulation with needles in alternating frequency of 15 and 30 Hz) was used to reduce pain in 50 adult patients with painful peripheral diabetic neuropathy, in a randomized, placebo controlled (sham - only needles) study, for 3 weeks⁽²⁷⁾. Each session was administered for 30 minutes, three times a week. Results demonstrated that the difference between pain intensity scores (measured through the VAS scale) between the treatment group (intensity of pain at first: $M = 6.2$, $SD = 1.3$ in the third week $M = 2.6$, $SD = 0.9$) and the control group (sham) (onset of pain intensity: $M = 5.2$, $SD = 1.6$ and after 3 weeks: $M = 4.8$, $SD = 1.2$), was significant. Significant difference was verified between pain intensity and the need for analgesics over time, showing that the treatment group required fewer analgesics and had a higher pain relief. Authors concluded that PENS is a useful therapeutic modality for non-pharmacological PDN pain relief, in addition to improving physical activity, bringing a well-being sensation, and quality sleep.

The study authors stressed that, although the precise mechanisms of analgesia provided by PENS are not entirely clear, they seem to be related to neural modulation and increased endogenous opioids⁽¹⁶⁾. Thus, through the cumulative effect of PENS over time, longer prospective studies may present better results, corroborating with experimental findings⁽¹⁴⁾ involving

electroacupuncture and TENS applied to animals with drug-induced diabetes.

Notwithstanding, electrical stimulation was also used to treat diabetic neuropathy pain in a randomized and controlled study, with a sample of 40 people, an average of 14.5 years of diabetes, and four years of diabetic neuropathy. Results in pain relief were no better than that obtained through the conventional treatment⁽²²⁾.

Reiki was another therapy used for the pain relief. In a randomized, semi double-blind, placebo controlled study⁽²¹⁾ performed with 207 individuals with type 2 diabetes mellitus, it was possible to observe that the difference between the pain relief reported by components of the two groups was not significant. Reiki is a manual therapy, based on the theory there is an intrinsic bioenergy in the human body that can be changed by practitioners of the therapy, providing relief from unpleasant symptoms⁽¹⁹⁾.

There was a significant pain reduction when the frequency rhythmic electrical modulation system (FREMS) was used PDN patients, aged between 18 and 70 years, who participated in placebo-controlled study. Moreover, authors showed improved function of peripheral nerves, and warned about the need for additional research to confirm the benefits of such therapy⁽²³⁾. A randomized, double-blind, placebo controlled study⁽¹²⁾ performed with a sample of 31 diabetics, with an average of 63.1 years old, and average disease existence of 15.9 years, showed increased skin blood flow at rest, after two series of ten treatment sessions, using the frequency rhythmic electrical modulation system (FREMS), applied in a random sequence, within 3 weeks.

The repetitive and cumulative exposure to pulsed electromagnetic fields (PEMF) at low frequency was also used in order to verify the effectiveness in reducing neuropathic pain in a multi-centre, randomized, double-blind, placebo-controlled study⁽²⁴⁾, with 225 individuals aged between 18 and 87, who had PDN (with moderate to intense pain – 4 or more in the VAS scale), for 6 months or more. Each patient used similar devices, generating PEMF or sham (placebo) for 2 hours a day on the feet, for 3 months, with a 1800-G dosimetry. They concluded that there was no positive effect on pain modulation considering time and dosimetry; however, they emphasized the importance of further research with larger dosimetries (3000-5000G) and longer exposure time, to investigate the influence of PEMF on nerve regeneration.

Among other non-pharmacologic therapies for PDN pain relief, it is relevant to mention the low-intensity laser, which has been used to treat chronic pain; nevertheless, in a study involving 50 individuals with diabetic neuropathy pain, the use of such therapy did not provide

significant relief, although there was a decrease of one point (+ / - 0.4) in pain scores measured by the Visual Analogue Scale after 4 weeks of treatment⁽¹⁸⁾.

Photostimulation has also been used as a treatment option for people with painful diabetic peripheral neuropathy. In a randomized, double-blind, placebo controlled study performed to assess the effect of such therapy over the intensity, quality of pain relief, and quality of life, the treatment group (n = 63) received four photostimulation applications, with a C3 DPN BiPhase, photo stimulator, and the control group (n = 58) was treated with placebo. Pain was assessed by means of self-reported (0-10 numerical scale) relief, through the Likert scale (0-5), the sensitivity was assessed through monofilaments, and the quality of life, using the SF-36. Authors concluded that four applications of photostimulation with IR resulted in significant pain relief (p < 0.0005), improved sensitivity and quality of life for individuals in the treatment group⁽²⁷⁾. The mechanism through which photo stimulation produces biological effects are not well known, however, evidence points to stimulation of mitochondrial cytochrome resulting in increased cellular activity and healing⁽²⁶⁾.

The effects of monochromatic infrared, were also investigated in a double-blind, placebo controlled study⁽²⁵⁾. Subjects received either an active infrared monochrome or a fictitious one for 2 weeks, and had limb sensitivity assessed through 5.07 and 6.65 Semmes Weinstein monofilament (SWM), and the Michigan Neuropathy Screening Instrument (MNSI). Among the 27 people who participated in the study, nine were insensitive to the SWM 6.65, and 18 were sensitive to this, but insensitive to the SWM 5.07. Pain, measured using a Visual Analogue Scale, decreased progressively for the group which was sensitive to the SWM 6.65, however, pain reduction was not significant for the group who was insensitive to this monofilament. Authors concluded that the treatment with monochromatic infrared improves feet sensitivity for individuals with peripheral neuropathy, concomitantly reducing neuropathic pain. It is relevant to mention that in a longitudinal study, with a cohort of 2239 participants

(average age 73 years), the monochromatic infrared (MIRE) provided a reduction of 4.8 points in pain (VAS score) and clinical improvement for feet sensitivity⁽¹⁵⁾.

Non-pharmacological therapies that provide improved feet sensitivity and result in significant neuropathic pain relief should be further investigated in order to elucidate their mechanisms of action, evaluate the effectiveness in different populations with and without PDN, evaluate the results of different dosimetries and treatment duration so that these therapeutic options can be safely used.

Therefore, further studies can contribute to the abandonment of ineffective therapies, preventing unnecessary direct and indirect costs to clients, families and health services, and unrealistic expectations that can generate frustration, lack of adherence to treatment, and negative repercussions in recovery and dealing with the condition.

Furthermore, studies have limitations related to the method, such as representativeness of the sample, length of treatment exposure, dosimetry, and pain measurement. However, it is encouraging to verify that a large number of people with refractory pain report improvements in quality of life through non-pharmacologic therapies, with reduced stress, improved circulation, sleep quality^(15, 17, 26-27), and sensitivity, which certainly impact on how the situation is faced, reducing morbidity and reinforcing adherence to treatment.

CONCLUSION

Studies have shown that non-pharmacologic therapies have been used for diabetic neuropathy pain, yet there is still a lack of consensus on their use as a therapeutic alternative to drugs. Several people with intense pain, after being exposed to treatment, reported improvements in sleep quality, sensitivity and stress reduction, impacting on quality of life. New researches, including treatments for a longer period of time, with dosimetry control, and representative samples are necessary to discover the actual importance of these therapies for pain relief.

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