Low Intensity Millimeter Wave as a Potential Tool in Treatment of Diabetic Sensorymotor Polyneuropathy

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Abstract

The purpose of this study was to determine the effectiveness of application of low intensity Millimeter Wave (MW) in treatment of Diabetic sensorimotor polyneuropathy (DSP).

We conducted a randomized sham-controlled single center study in 51 patients with painful DSP diagnosed according to Toronto Clinical Neuropathy Score (TCNS). Patients were randomized to receive either sham or MW treatment over 2 weeks period, 6 times per week. The primary efficacy parameter was the difference in TCNS after 2 weeks.

The patients had similar baseline characteristics for TCNS, HbA_{1c} and duration of DSP. After 2 weeks of treatment both groups had a reduction in TCNS ,in MW-treated group the mean of TCNS decreased to7.58 compared with 9.56 for the Sham group(p=0.033). MW had no effect on nerve conduction studies.

The obtained data allow us to suggest the MW-treatment as a promising tool for Diabetic Sensorymotor Polyneuropathy therapy.

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Introduction

DIABETES MELLITUS is the most common cause of neuropathy in the world[1]. Diabetic sensorimotor polyneuropathy (DSP) is the most common complication of both type 1 and type 2 diabetes. In many patients with DSP, pain will develop at some time during the course of the disease [2].

In a cohort of 4400 patients with diabetes studied for 20 to 25 years, 45% developed neuropathy during the course of their disease[3].

Pain due to diabetic neuropathy affects the feet and ankles most often and, to a lesser extent, lower extremities above the knees and upper extremities[4]. The pain may be severe and often has an unusual "dysesthetic" quality. If inadequately treated, it is frequently associated with mood and sleep disturbances. Attempts to treat diabetic neuropathies can be divided into those directed at modification of the underlying disease process and those directed toward symptom suppression. Improved glycemic control is the mainstay of efforts to modify the incidence and course of the disease, although aldose reductase inhibitors may also play a role[5-8].

Painful DSP is often resistant to treatment with simple analgesics. Medications such as narcotic analgesics, tricyclic antidepressants, anticonvulsants (phenytoin and gabapentin), phenothiazines, antiarrhythmics, nonsteroidal anti-inflammatory drugs, and opioids have all been used with limited success in treating painful DSP. In addition, adverse effects such as drowsiness, lethargy, and unsteadiness are frequent and limit the use of pharmacologic interventions. Nonpharmacologic therapies, such as low-intensity millimeter wave (MW) may be effective adjunctive or alternative treatments for painful DSP with avoidance of systemic drug adverse effects.

At present the Low-intensity Millimeter Wave (MW) therapy is widely used for the treatment of a large variety of diseases including cardiovascular disorders, diabetes, dermatitis, gastrointestinal disorders, wound healing, pain relief, and the reduction of toxic side effects of chemotherapy in cancer patients[9,10].

Previously the studies conducted at UNESCO Chair-LSIPEC have shown that MW had depressing

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effect on cell membrane excitability and chemosensitivity, which were realized through cell swelling[11]. At the same time it is known that cell pathology (including diabetes) is accompanied by cell over hydration[12-14]. The fact that neuronal hydration brings to the increase of its excitation, in the result of increasing of the number of ionic channels functioning in membrane[15], the over-hydration induced over-exitation of neurons was suggested as the main mechanism of pain (nococeptive) signal generation[16, 17].

Thus, on the basis of these data it was suggested that MW-induced cell dehydration could have pain relief effect and it could be used for therapeutic treatment of Diabetic Sensorimotor Polyneuropathy as well. For testing this hypothesis, the effectiveness of application of MW (61.2 GHz modulated by 4 Hz Electromagnetic Fields) in treatment of DSP patients was studied.

Methods

The study was conducted at the Medical University of Babol (Babol, Iran) in the Diabetic clinic, and was approved by the university Research Ethics Committee and all patients provided written informed consent prior to study participation.

A total of 51 patients with painful DSP were enrolled in the study. Eligible patients included men and women aged more than 40 years who had DSP for at least 3 months. Diagnosis of DSP was based on the Toronto Clinical Neuropathy Score (TCNS) presented on Table 1.

It was required that pain be present in both feet. Patients with an average TCNS of at least 5, and analgesic or adjuvant analgesic medications (e.g., opiates, antidepressants, anticonvulsants, local anesthetics) were allowed but was unchanged for at least 4 weeks before entering the study and for the duration of the study.

Exclusion criteria included the presence of other severe pain that could confound assessment or self-evaluation of the pain due to diabetic neuropathy, unstable medical conditions (e.g., malignancy, active/untreated thyroid disease) or other neurologic diseases that would confound assessment of neuropathy, pregnancy, metallic implants, alcohol or illicit drug abuse. Medication dosages for diabetes control were to remain stable during the study.

The low intensity MW generator “Artsakh-03m” (“Rikta-Center” LLC, Russian Federation), designated for clinical application was used.

The MW which was used in our work, for clinical treatment had the following parameters: intensity – 5.83 mW/cm^2, frequency- 61.2 GHz (wavelength -4.9 mm), modulated by 4Hz EMF, distance between antenna and patient’s skin was ~2mm, and radiation painful zone was ~ 2 cm^2 area of skin, exposure time- each day per 15 min.

Neither the patients nor the evaluating clinicians knew which treatment was active and which was sham. Both groups were exposed to the same instrument but the “START” button was in “off” position for the Sham group. Physical and neurologic examination for stratifying TCNS and Nerve Conduction Studies (NCSs) were performed in all patients upon entry into the study and after the treatment phase (2 weeks). Medical history, demographics, were initially performed on all eligible patients and HbA_{1c} was measured too. Conventional NCSs were administered using a standard testing protocol in the legs. Studies included testing of bilateral peroneal and tibial motor nerves, sural sensory nerves in the lower limbs. Neurologic examination and NCSs were conducted by an independent observer who was masked to all other results. 51 patients (25 patient in active treated group and 26 in sham treated group) with painful DSP. were randomized to receive either sham or active treatment during two weeks. Treatments were administered six times weekly and were applied to an area of pain along the sole or dorsum of the foot.

After 2 weeks of treatment the efficacy of treatment was determined with respect to changes from baseline in TCNS and NCSs parameters.

STATISTICS

Statistical analyses were performed with SPSS software (version 13.0). The TCNS changes between two groups were compaired by Man-whitney test and change from baseline was compared by Wilcoxon signed –rank test in both group. NCSs and other variables were analyzed using t-test and paired t-test.

Results

A total of 51 patients (40 women and 11 men) were enrolled in the study. The demographic profile is shown in Table 2. All patients, except one, had type 2 diabetes mellitus. The baseline demographics were the same in both groups, at baseline there was statistically no significant differences in Toronto clinical neuropathy score (TCNS), age, duration of diabetes, type of diabetes and HbA_{1c} between the two groups (Table 2).

After two weeks of treatment mean TCNS decreased from 11.56 to9.48 (p=0.000) in sham treated group, and from 11.58 to 7.32 (p=0.000) in active treated group. The mean TCNS in active treated group was significantly lower than in sham

group (7.32 vs 9.48, p=0.033) (Figure 1).

The mean decrease from baseline in active treated group (4.26) was significantly higher than in sham group (2.08).

After two weeks intervention NCSs had not significant changes, during intervention pulse rate respiratory rate, blood pressure remained stable but blood pressure decreased ~1 to 2 mmHG in four patients from active treated group. The therapy had no adverse effect on patients.

Symptom scores	Reflex scores	Sensory test scores
Foot pain	Knee reflexes	Pinprick
Numbness	Ankle reflexes	Temperature
Tingling		Light touch
Weakness		Vibration
Ataxia		Position sense
Upper limb symptoms		

Table 1. Toronto Clinical Neuropathy Score

Symptom scores: present = 1, absent = 0; reflex scores: absent = 2, reduced = 1, normal = 0; sensory test scores: abnormal = 1, normal = 0; total scores range from normal = 0 to maximum of 19

	Sham treated Group	Active treated Group
Number of patients	26	25
Sex (men/women)	2/24	4/21
Type of diabetes (1/2)	1/25	0/25
Duration of diabetes (years)	13.8 ± 10.8	12.6 ± 9.2
HbA_{1c} (%)	8.2 ± 1.5	7.8± 1.4
Duration of pain (years)	5.2 ± 4.1	5.3 ± 3.6
Height (cm)	165±13	162±13
Weight (kg)	75.5± 8.5	76.5 ± 5.5
Toronto Clinical Neuropathy Score before treatment	11.58 ± 3.57	11.56 ± 3.59

Table 2. Baseline demographics of 51 patients with painful DSP
Data mean ± SD

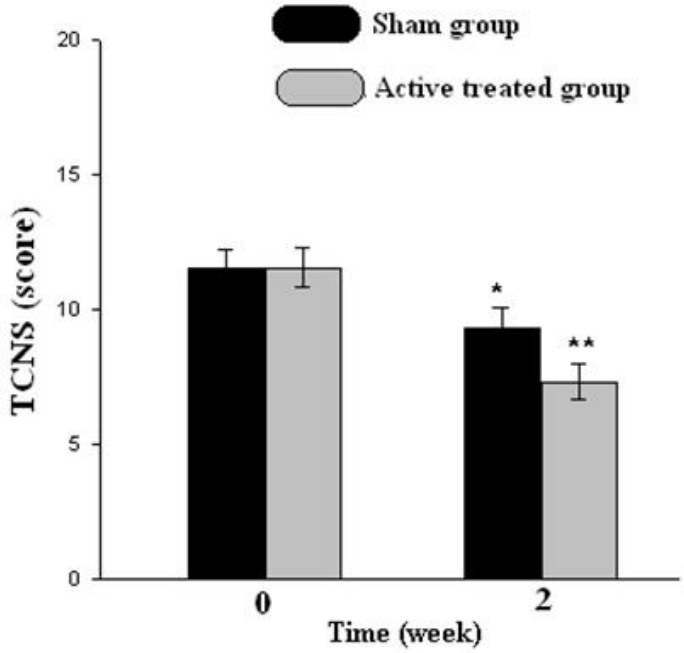

Figure 1. TCNS decreased in both sham and active treated group after two weeks treatment but it was more for active treated group ,TCNS expressed here as mean-+SEM , * P<0.05, ** P<0.005.

Discussion

Neuropathies are among the most common of all the long-term complications of diabetes, affecting up to 50% of diabetic patients[18-21]. Whereas some patients may have extremely painful symptoms, others with a more marked neuropathic deficit may be asymptomatic.

Neuropathic pain is often refractory to multiple pharmacologic interventions, and their use can be limited by adverse effects. Nonpharmacologic treatments lack systemic adverse effects, but efficacy over a simple placebo response optimally should be demonstrated in controlled clinical trials.

Although the exact mechanism of non thermal biological effect of MW on cells and organisms is not clear yet, the latter is widely used for therapeutic purposes as anti-inflammatory and hypoalgesic factors[22, 23], modifying the immune status of an organism[24], improving microcirculation in injured tissues and stimulation physiological and reparative regeneration[25].

It is documented that diabetes are accompanied by cell hydration, while the factors having therapeutic effect cause the body cell dehydration[26, 13, 27]. As cell overhydration causes its over-excitation (pain signal generation)[17], the DSP could be considered as a result of nerve tissue over-hydration. Our recent work on dehydration effect of MW on cell and tissue[11] allow to predict that MW could have pain relief effect.

In the present work were tested the MW radiation effect on patients with DSP. As expected, a placebo response was observed in sham treated group ,however In active treated group TCNS was reduced from 11.56 to 7.32, compared with the Sham-treated group (11.58 to 9.45) (Figure 1).

It is known that the placebo effect have a positive emotional (hormonal) nature and it could have at least 33% of clinical improvement in patients with various diseases[9]. The obtained results, demonstrating statistically significant changes in TCNS in all patients regardless of treatment arm, but also our results shows a reduction in TCNS of 36.6% and 18.3% in active and sham treated group respectively ,that could be the real effect of MW in addition of placebo effect .

In this study, randomization produced a difference in the proportion of men and women in each group. One might hypothesize that differences in sex response to placebo may have confounded the results. The large meta-analyses have been conducted investigating sex response rates to placebo in patients with pain[29] concluded that sex does not predict placebo response or duration.

Some clinical results indicate that the central nervous system participates in response to MW stimuli; for example, electroencephalogram changes

were registered in healthy volunteers[30] and children with cerebral palsy[31] as a result of their exposure to MW.

The nerve conduction study shows that MW exposure has not significant effect. Probably, it could be explained by short period MW exposure. If MW was proven to be effective in future controlled studies, the design of home MW equipment might be advantageous to facilitate patient compliance.

The data obtained in present work shows no significant adverse effect. Although slight paresthesias, previously mentioned in several case reports and non-controlled case series[32, 33], but in our study, no patient developed paresthesis during treatment with MW but also some of them reported relieved paresthesis.

Slight paresthesias, previously mentioned in several case reports and non-controlled in our experiments the blood pressure decreased 1 to 2 mmHG in four patients in active treated group. It has been shown that static magnetic field could decrease blood pressure[34], but for final conclusion on the possible effect of MW on blood pressure we need to conduct more detailed investigation.

This study demonstrated a significant reduction in TCNS with MW, compared to Sham group. We conclude that there is promising data from our small randomized controlled trial for beneficial effects of electromagnetic millimeter waves in frequency range 60 GHz on DSP. We believe that large-scale randomized controlled trials on the effectiveness of this non-invasive therapeutic technique would be worthwhile because peripheral diabetic neuropathy and painful diabetic sensorimotor polyneuropathy is common, no significant adverse effects were observed with MW and current pharmacologic treatments are variably effective medication adverse effects limit their use.

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