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Does Electroanalgesic Therapy Decrease Neuropathic Pain in Diabetic Patients?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not use of electroanalgesic therapy decreases neuropathic pain symptoms in diabetic patients

STUDY DESIGN: Review of a 2 randomized control trial published in 2013 and 2011 published in the English language and an observational study published in 2010 in the German language translated into English.

DATA SOURCES: One randomized, double-blind control trial comparing frequency-modulated electromagnetic stimulation vs placebo in reduction of diabetic neuropathic pain, one randomized, control trial comparing microcurrent transcutaneous electric nerve stimulation vs placebo in reduction of painful diabetic neuropathy and a observational study using baseline comparison of the observed group at the beginning of the treatment vs the end of the treatment.

OUTCOMES MEASURED: Pain is measured through various scales administered in their respective studies. The Visual Analogue Scale was used to measure day and night pain, the Neuropathic Pain Score administered to assess pain intensity and the Thermal Sensory Analyzer to assess cold, warmth, cold pain and heat pain.

RESULTS: Bosi et al. demonstrated significant reduction in day and night pain in treatment group vs placebo group. Gossrau et al. did not conclude that applied transcutaneous electrotherapy showed superior reduction of pain compared to placebo group. Moharic and Burger concluded there were no statistically significant changes or thermal pain perception thresholds after transcutaneous electrotherapy.

CONCLUSIONS: Although some pain relief was reported by participants in these studies, collectively, all three studies have were unable to exhibit significant evidence of lasting DPN pain relief using electroanalgesic treatment.

INTRODUCTION

Peripheral neuropathy is a common complication in diabetes type 1 and type 2 patients that often manifests as pain, paresthesia, and numbness in their upper and lower extremities.[1,2] The pathology of diabetic peripheral neuropathy (DPN) is complex and primarily involves atherosclerosis of the endoneural vascular supply leading to nerve ischemia and axonal atrophy.[2,3] Diabetic peripheral neuropathy (DPN) typically presents as a loss of sensation beginning in the toes and progresses proximally. Patients often describe chronic neuropathic pain as burning, pins and needle tingling, and diffuse aching.[1] Hyperalgesia, allodynia and loss of balance and coordination are also complaints associated with DPN.[6] Manifestations of symptoms range from mild to severe and in some cases physical debilitation.[6]

25.8 million people in the United States have diabetes and 79 million people are prediabetic. It is estimated that 60-70% of diabetes patients suffer some form of neuropathy. 27% of direct medical cost of diabetes is attributed to diabetic peripheral neuropathy totaling a cost of $10.9 billion dollars spent annually on treatment.[5] Although the mechanism of the disease is poorly understood, it is widely thought that hyperglycemia causing changes in the blood vessels supplying the peripheral nerves underlie the mechanisms involved in microvascular damage and hypoxia.[7]

Management of painful DPN poses a large challenge to the medical community.[3] Current treatment only reduce associated symptoms by 30-50% and due to lack of sufficient knowledge concerning the pathogenesis of the disease there are no curative treatments that can fully provide complete relief of symptoms.[7] There are five main classes of medications used for the management of peripheral neuropathic pain: tricyclic antidepressants, anticonvulsants, serotonin-

norepinephrine reuptake inhibitors, opiates and topical analgesics.[7] Medications are the mainstay of DPN treatment but they are unsuccessful in providing larger numbers of relief notwithstanding the long list of adverse effects and complex drug interactions for patients on medications for comorbid conditions.[7]

Based on the gate control theory electroanalgesic therapy is being explored in providing a physiological block and activating an pain inhibitory system as a means to address the neuropathic pain in diabetic patients.

OBJECTIVE

The objective of this systematic review is to determine whether or not electroanalgesic therapy decreased neuropathic pain in diabetic patients.

METHODS

The populations chosen were diabetic patients $\geq$ 18 years old who suffer from peripheral neuropathic pain with the studies further selecting subjects with symptomatic DPN affecting the lower extremities that have suffered symptoms more than a year. The intervention in all studies were electroanalgesic therapy via micro-transcutaneous electrical nerve stimulation (TENS) units or frequency modulated neural stimulation (FREMS) units.[1]

Key words used in the searches were “diabetic neuropathies”, “transcutaneous nerve stimulation”, and “electroanalgesia”. All articles were published in peer-reviewed journals and in the English language with one article translated into English from the German language. The author searched the articles through PubMed and selected articles based on the relevance to the clinical question, human subjects and the outcomes that included patient-oriented evidence that

matters. Inclusion criteria consisted of studies where design was either observational or randomized, single blinded or double blinded, placebo controlled, studies that included diagnosis of diabetes mellitus type 1 or type 2 for at least 1 year, patients who experience symptomatology of painful diabetic neuropathy, and patients $\geq$ 18 years of age. In the study conducted by Bosi et al, further selection of participants included patients with a HbA_{1c} <11.0%, abnormalities in amplitude, latency or conduction velocity in at least one motor nerve, and a Michigan Diabetes Neuropathy Score (MDNS) equal or greater than 7 points.[1] Exclusion criteria in this study consisted of patients with previous treatment with TENS or other electrotherapy for DPN, implantable pacemaker, defibrillator or neurostimulator, presence of active foot ulcer and/or previous major amputation of lower extremities and any concomitant sever disease limiting compliance to study procedures or life expectancy. The criteria for patients selected in the Gossrau et al study included a HbA_{1c} <8.0%, gammaglutamyltransferase (GGT) <1.4 µmol/L, normal creatinine and blood cell counts; and current pain intensity of at least 4/10 on a numerical rating scale (NRS).[2] The exclusion criteria in this study consisted of patients with implanted pacemakers, heart defibrillators, brain stimulators, history of alcohol abuse and malignancies.[2] Selection of patients in the Moharic and Burger study was made at an outpatient clinic for diabetic foot with diabetes mellitus type 2, further selecting patients who agreed to at least two items of the Michigan Neuropathy Screening Instrument (MNSI).[3] The exclusion criteria in the Moharic and Burger study included patients with other non-diabetic neuropathies, significant pain of other etiologies or peripheral vascular disease.

In the study conducted by Bosi et al treatment was administered via the Aptiva device.[1] Four pairs of electrodes were applied to both lower extremities and biphasic sequences of asymmetric and electrically balanced pulses with an active phase of high negative voltage spike

(-300V) and short duration 10-100 microseconds proceeded by a recharging phase of low voltage and long duration (.9-999ms) with variable pulse frequency 1-1000Hz were applied to treatment groups.[1] Electrodes were also applied to the placebo group but no electrical impulses were administered. FREMS or placebo treatments were 30 minutes in length and completed sessions consisted of 10 consecutive treatments administered at least 24 hours a part within a 21 day time frame.[1] Studies by Gossrau et al. were conducted over a 4 week period consisting of 3 visits per week. The treatment group were administered 30 minutes of low-frequency microcurrent (30-40 microA) via skin electrodes placed on the proximal dorsum pedis and on top of caput fibulae on both legs. In the placebo group the electrodes were not connected to the TENS unit-microcurrent and did not induce sensations or muscle twitching.[2] Duration of the study consisted of 3 visits over a 4 week period. In the last study reviewed by Moharic and Burger titled, transcutaneous electrotherapy was administered to patients by portable unit generating current with a pulse width of 30-260ms, intensity 0-14mA and frequency 2-150 mHz in constant, burst or modulated form. 5 x 5cm self-adhesive PALS electrodes placed proximally 10 cm above internal or external malleolus and distally in the sole or dorsum of the foot, alternating the two configurations each day on both lower extremities x 3 consecutive hours daily for 3 weeks.[3]

OUTCOMES MEASURED

Outcomes measured in these studies were all based on the reduction of pain scale rating reported by patients. Other outcomes measured were cold, warm, cold pain and heat pain thresholds, vibration perception thresholds and touch perception thresholds, pain intensity, pain interference with activity of daily life and depression and tactile sensations. Indices utilized to measure outcomes were: Thermal Sensory Analyser, Vibratory Sensory Analyser, Von Frey's hair, Pain Disability Index, Neuropathic Pain Score, Center for Epidemiologic Studies

Table 1: Demographics and characteristics of included studies

Study	Type	#Pts	Age years	Inclusion Criteria	Exclusion Criteria	WD	Interventions
Gossrau[1]	RCT	41	67+_12	diagnosis of type 1 or type 2 diabetes mellitus for at least 1 year and have painful diabetic neuropathy (PND), diagnosed by an experienced neurologist or diabetologist, HbA1c <8%, GGT < 1.4µmols/L, normal results for creatinine and blood cell counts; and current pain intensity of at least 4/10 on a numerical rating scale (NRS)	implanted pacemaker, heart defibrillator, brain stimulator, history of alcohol abuse and malignancy	0	4 weeks, 3 visits/week, tx group: 30 mins of low-frequency microcurrent 30-40 microA via skin electrodes places on proximal dorsum pedis and on top of caput fibulae on both legs Placebo group: Identical to treatment group but electrodes not connected to micro-TENS unit
Bossi[2]	RCT	164	18-75	Patients with documented type 1 or type 2 diabetes >1 year and HbA1C , 11%, DPN affecting LEs with at least one positive sensory symptom, abnormalities in amplitude (<6mV), latency (>6.5ms) or conduction velocity (<40m/s) in at least one motor nerve (tibial or deep peroneal) and/or in sural nerve, measurable sensitive NCV and evocable potential in the sural nerve, a MDN Score ≥7 points, stable dose of pain medications or other diabetic neuropathy medications during month leading up to enrollment	Previous tx with TENS or other electrotherapy, implanted pacemaker, defibrillator or neurostimulator, presence of active foot ulcer, amputation of LEs, concomitant severe disease limiting compliance to study procedures or life expectancy	54	Treatment with FREMS (biphasic sequences, asymmetric and electrically balanced pulses with an active phase of -300V and short duration proceeded by a recharging phase of low voltage and long duration; variable pulse frequency 1-1000Hz.) Placebo – no electrical pulses FREMS and Placebo administered via Aptiva device: 4 pairs of electrodes applied to LEs
Moharic[3]	RCT	46	43-75	Diabetes mellitus type 2, stable glycemic control, chronic PDN (at least 6 months) in LEs, at least two items of the MNSI, one relevant to general asthenia and one relevant to perivascular disease.	patients with other non-diabetic neuropathy, significant pain of other etiology or peripheral vascular disease	0	Portable TENS unit, pulse width of 30-260ms, intensity 0-14mA and frequency 2-150 mHz in constant, burst or modulated form.

Depression Scale, Visual Analogue Scale, Semmes-Weinstein monofilament test. For the purpose of comparison of studies in this review, focus is geared towards indices measuring pain.

RESULTS

The Bosi et al study was a double-blind, placebo controlled RTC. Assignment of patients to treatment were randomized and the randomization allocation were concealed from those enrolling the subjects into the study.[1] 110 patients were found eligible for the study and 54 were randomly assigned to receive FREMS and 56 received placebo.[1] Assessments of participants were collected 8 times over a 51 week period. All patients were analyzed in the groups they were originally randomized into.[1] At the conclusion of the study, 32% of subjects were lost and a "worst-case" analysis was not completes on subjects lost.[1] The study showed that both the VAS score for nighttime pain and daytime pain were significantly reduced in the intention-to-treat population compared to the placebo group.[1] Reduction of >30% or >50% scoring was significantly higher in the FREMS treatment group in comparison to the placebo group after the second and third treatment sessions.[1] Data in the study was continuous showing an average change in VAS scoring between treatment and placebo groups and authors reported outcomes through a change in mean from baseline (baseline values shared in table 2).[1] The precision of the estimate of the treatment effect was P=0.02 which demonstrates statistical significance.[1] This trial confirms safety and efficacy of FREMS in reducing pain in diabetic patients with PDN. [1]

Table 2: Baseline characteristic of study participants (values as mean with standard deviation)[1]

Baseline Characteristics	Placebo (n=51)	FREMS (n=50)
Night-time pain, VAS score	45.2±29.6	41.3±29.7
Day-time pain, VAS score	40.9±24.0	31.6±26.3

The Gossrau et al study included 41 patients, 22 in the treatment group and 19 in the placebo group.[2] Characteristics such as body mass index, duration of diabetes and PDN symptoms and HbA1c of patients were equally distributed through the treatment and placebo group.[2] Randomization allocation was concealed and intention to treat analysis was applied to the summation of scoring submitted by patients. Scores from the Neuropathic Pain Scale (NPS) and Pain Disability Index (PDI) were compared before treatment, after treatment and a month following completion of the treatment.[2] There was no significant difference between the treatment and placebo group after the first two measurements($P>0.18$).[2] There was also no significance found in the comparison of the NPS score at the beginning of treatment and after the follow-up visit a month after treatments ended ($P>0.5$).[2] None of the treatment effects showed evidence of precision because they all exceeded p-value.[2] The relative risk ratio (RRR) was calculated to be -0.48, the absolute risk ratio (ARR) -0.253, and the numbers needed to treat (NNT) -4 show a small treatment effect.[2] For the PDI score, table 3 displays that the items of the PDI were not influenced by the micro-TENS treatments.

Table 3: PDI score not influenced by micro-TENS (values as mean with standard deviation)[2]

	Treatment Group before treatment – T1	Placebo Group before treatment – T1	Treatment Group after 4 weeks treatment	Placebo Group after 4 weeks treatment	Treatment group after 1 month follow-up	Placebo group after 1 month follow-up	P value difference T1/T2	P value difference T1/T3
PDI	22.05± 16.5	21.79± 15	17.7± 15.5	18± 14.6	19.45± 15.6	18.05±13.5	P > 0.8	P > 0.5

The Moharic and Burger study was an observation study with 46 participants.[3] Outcomes assessed were cold pain and heat pain thresholds and comparisons of outcomes at the beginning of treatment and 1 month after completion were assessed reporting change in mean from baseline.[3] Cold and heat pain were measured at four sites: the thenar eminence, dorsum of the

foot, 5cm below the fibular head and the anterior part of the thigh.[3] Change in thenar cold and heat pain were the only two significantly changed thresholds with p-value of 0.0001 as seen in table 4.[3]

Table 4: Results from statistical tests of sensory thresholds (thermal thresholds in °C)[3]

	Threshold	Baseline Median	After treatment Median	One Month after treatment Median	P value
Thenar	Cold pain Hot pain	4.1 47.4	13.2 45.0	15.9 44.5	0.0001* 0.0001*
Dorsum of foot	Cold pain Hot pain	0.0 50.0	0.0 50.0	3.5 50.0	0.2044 0.7922
Lateral part of leg	Cold pain Hot pain	2.7 50.0	1.6 49.5	9.9 48.6	0.1202 0.1566
Anterior part of thigh	Cold pain Hot pain	2.2 47.7	8.1 47.9	12.1 47.4	0.1306 0.3944

DISCUSSION

All three studies were unable to exhibit evidence of lasting DPN pain relief using electroanalgesic treatment. In the Bosi et al study, there was a notable reduction in the VAS scoring at the conclusion of the study however, the pain reduction was not sustained as many patients returned to baseline scoring discovered during a 3 month follow up survey.[1] In the Gossrau et al study, the lack of significance found after NPS comparisons between treatment and placebo group exhibited no difference in reduction pain intensity, pain tolerance and presence of burning or stabbing pain quality after treatment with the TENS unit. The lack of significant differences in outcomes showed that general reduction of pain when applying TENS is not a superior treatment to the placebo treatment.[2] Moharic and Burger also concludes the that TENS did not display significant findings regarding baseline pain thresholds compared to post treatment thresholds.[3]

Each study had a limitation in design and implementation of investigation. The Bosi et al. study had a limitation on their inclusion criteria selecting patients who demonstrated mild symptomatology excluding diabetic patients with more severe symptoms therefore, possibly excluding the findings of the study's application to this population.[1] In the Gossrau et al study, the lower intensity of the currents in a micro-TENS units versus a conventional TENS unit could be attributed to the low therapeutic efficacy of the treatment.[2]

CONCLUSION

Two RCTs and one observational study were systematically reviewed for the effectiveness of electroanalgesic therapy decreasing neuropathic pain in diabetic patients. Collectively, these studies do not support the efficacy of this modality in the treatment of diabetic peripheral neuropathic pain. However, the Gossrau et al and Mohari and Burger studies found lack of significance in comparison groups limitations in the inclusion criteria as well as the inconsistencies in the modalities of electroanalgesic therapies used across all three studies, there does remain the question if the ineffectiveness of this treatment is deemed as a conclusive finding. The safety of electroanalgesic therapy has been demonstrated in all three studies but evidence of the efficacy of these treatments is lacking. Generally, any evidence of treatment for diabetic peripheral neuropathic pain is quite limited. There are currently a relatively small number of studies published on this mode of DPN treatment.

Future study is warranted to evaluate electroanalgesic therapy in a more consistent and comprehensive evaluation in modality and in the breadth of patient population. In terms of safety, efficacy and cost it would be of great benefit for future studies to address comparisons of therapies such as cost-effectiveness studies of the different treatments as to provide more

information to prescribing physicians and to diabetes patients while exploring the best options for treatment.

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