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A Randomized, Sham-Controlled, Double-Blind Pilot Study of Pulsed Electromagnetic Field Therapy to Evaluate Small Fiber Nerve Growth and Function and Skin Perfusion in Subjects with Painful Peripheral Diabetic Neuropathy

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Abstract:

Purpose: The objective of this study was to determine the potential efficacy and safety of dual energy pulsed electromagnetic field therapy (PEMF) on painful distal symmetric diabetic sensorimotor polyneuropathy (DSPN).

Methodology: Subjects with Type 2 diabetes and painful DSPN were randomized to receive either an active or sham PEMF device. Objective measures of efficacy (skin biopsy, nerve conduction velocity (NCV) studies, dorsal and plantar foot skin perfusion pressure (SPP) were performed prior to and following 60-days of twice daily 30 minute treatments. Patient reported outcomes included perception of pain, concomitant medication use and adverse events.

Major findings: Dorsal foot SPP improved with PEMF (n=11), change from baseline=19.6 mmHg) vs. sham (n=7, change=-17.4 mmHg), p=0.03. Trends in favor of PEMF vs sham were observed for medial nerve (n=4), planter nerve (n=4) and sural nerve (n=15) onset time and amplitude (p>0.05) other than medial planter onset time (p=0.04). Although change in pain scores were similar, compliance with device use was higher in the active group compared to the sham control. The series of tests and long-term use of PEMF was well-tolerated and feasible. No device related adverse effects were recorded.

Principal conclusions: Twice daily PEMF therapy was feasible, well-tolerated, and associated with trends suggesting improved nerve function and microcirculation in patients with painful DSPN. Future, large randomized controlled trials are necessary to confirm these findings and evaluate the potential longer term benefits on symptoms and pathology of DSPN.

Keywords: Diabetes; Nerve conduction velocity; Peripheral neuropathy; Pulsed electromagnetic field; Skin biopsy; Skin perfusion pressure

Key Messages

Painful diabetic neuropathy affects the majority of patients with diabetes during their lifetime. The presence of diabetic neuropathy increases the potential for diabetes-related lower extremity complications.

The aim of this randomized, sham-controlled trial was to determine the feasibility and effects of 60 days of treatment with PEMF therapy on skin perfusion, nerve growth and function as well as pain perception, compliance and safety in subjects with painful diabetic neuropathy. Nineteen patients (12 active; 7 sham) participated in this study.

This pilot study demonstrated feasibility of use and trends in favor of PEMF in nerve function and skin perfusion of the dorsal foot. Although a reduction in average pain intensity score was not observed, subjects in the active group were relatively more compliant with device use. No device adverse effects were reported.

Introduction

Peripheral neuropathy will occur in the majority of people with diabetes mellitus during their lifetime [1]. Of the various types of diabetic neuropathy that exist, distal symmetric sensorimotor polyneuropathy (DSPN) is the most common, accounting for up to 75% of all diabetic-related neuropathies diagnosed in the US [2,3]. DSPN initially affects the smaller unmyelinated C fibers in the hands and feet, which controls light touch, pain and temperature sensation before progressing to the larger myelinated A delta fibers which convey vibratory sensation, proprioception and joint position [4,5]. Advanced DSPN leads to the loss of protective sensation, a precursor in the development of Charcot deformities of the foot and one of the components in the triad of diabetic foot ulceration (DFU) development, both of which are associated with increased morbidity, mortality and healthcare costs [3,6-8]. In addition, up to 50% of patients have painful DSPN with those with Type 2 diabetes affected more often than those with Type 1 diabetes (90-90% vs. 5-10%) [4,5].

Pain associated with DSPN is described as burning, lancinating, tingling, and shooting and is often worse at night. Hyperalgesia and allodynia may also be present [2,4]. Pain interfered with activities of daily living and is associated with disability, psychosocial impairment, and a reduced quality of life [2,4,9].

First line treatment to assist with prevention and/or delay in progression of DSPN is patient education, glycemic control, and lifestyle modifications. Pharmacotherapy is often employed if painful DSPN is present [2-4]. The US Food and Drug Administration (FDA) has currently only approved two agents for the treatment of painful DSPN, duloxetine and pregabalin. Tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and anticonvulsants, are also prescribed for pain [2,3]. The aforementioned medications have been reported to improve pain scores by 30 to 50%, although adverse effects can result in discontinuation of use in up to 50% of patients [1,3,11]. While topical analgesics have been reported to have similar effects on pain reduction with less systemic side effects compared to systemic pharmacotherapy, their use is limited by low patient compliance with application and limited efficacy [10,11]. Electrical nerve stimulation, acupuncture, electro acupuncture, cognitive behavioral therapy, biofeedback, and physical therapy have also been reported to reduce painful DSPN [12-19].

Modality	Comments
Patient education	
Glycemic control	
Lifestyle modifications, i.e., diet and exercise	
Pharmacotherapy	Duloxetine – FDA approval for treatment of painful DSPN
	Pregabalin – FDA approval for treatment of painful DSPN
	Tricyclic antidepressants
	Selective serotonin reuptake inhibitors
	Serotonin-norepinephrine reuptake inhibitors
	Anticonvulsants
	Opiods
Topical therapies	Topical analgesics, i.e., lidocaine patches, capsaicin ointment
Other modalities	Electrical nerve stimulation
	Acupuncture/electroacupuncture
	Cognitive behavioral therapy/biofeedback
	Physical therapy

Table 1: Treatment for painful distal symmetric sensorimotor polyneuropathy (DSPN).

Brief Review of the Literature

Pulsed electromagnetic field (PEMF) therapy is currently indicated for adjunctive use in the palliative treatment of postoperative pain and edema of the soft tissues. A meta-analysis of PEMF use reported evidence of the effectiveness of this therapy in the treatment of postoperative and non-postoperative pain and edema and wound healing [20]. Previous in vitro and in vivo studies suggest that PEMF modulates pain signaling through activation of peripheral endogenous opioids [21,22]. Given the previously described morbidity of diabetic peripheral neuropathy, use of a noninvasive device that may reduce symptoms can be considered a desirable option for those suffering from DSPN [2,3]. The objectives of this pilot study in subjects with painful DSPN included the following: (a) determine the feasibility and effect of multiple objective endpoints related to skin perfusion, intraepidermal nerve fiber growth and alternations in nerve function, (b) obtain preliminary patient reported outcome assessments of acceptance, compliance and perception of pain, and (c) examine for any potential safety issues.

Methodology

This was an IRB approved, two center, randomized, double-blind, sham-controlled clinical trial conducted with 22 subjects with DSPN performed between July 2015 and September 2016 (NCT03077893). The trial was performed in accordance with the ethical guidelines set for by the 1975 Declaration of Helsinki. Subject who participate d in the study met the inclusion and exclusion criteria outlined in Table 1 and provided written informed consent. Subjects were allowed to continue taking analgesic medications, including opioids, no steroidal anti-inflammatory agents, antidepressants and muscle relaxants, as prescribed on a routine basis or as needed for pain symptoms. Concomitant use of transcutaneous electrical neurostimulators (TENS units), implanted neurostimulators, local injection, intrathecal infusion, or acupuncture was not allowed. Subjects were randomized 2:1 to receive active treatment with dual field PEMF therapy (Provant® Therapy System, Regenesis Biomedical, Inc., Scottsdale, AZ) or an identical inactive sham device.

Inclusion Criteria	Exclusion Criteria
≥ 22 and<80 years of age	Type 1 diabetes
Documented Type 2 diabetes	Open ulcer on the target extremity
HgbA1c<10% within the previous 90 days	Peripheral arterial disease (ABI >1.40 or<0.90)
Peripheral diabetic neuropathy with pain, numbness, tingling, and/or burning in at least one foot	Venous insufficiency (CEAP grade C6)
Pain Phase 2, 3, or 4.	Total foot thickness>6 cm
	Previous nerve decompression surgery of the target extremity
	Previous treatment with PEMF therapy on the target extremity within the previous 6 months

	Systemic corticosteroids use with the previous 90 days Contraindications to PEMF Local injection performed in target extremity in the previous 30 days or 6 weeks if long acting lidocaine products used

Table 2: Key inclusion and exclusion criteria.

Assessments

A skin biopsy, skin perfusion pressure (SPP) and nerve conduction velocity (NCV) with or without a sympathetic skin response (SSR) was performed on Day 0. A 3mm punch biopsy of the skin was obtained from the first web interspace on the dorsal aspect of the foot to determine small fiber innervation within the distribution of the deep peroneal nerve. Immunocytochemistry evaluation of the specimen with PGP-9.5, an axonal protein, and evaluation of the number and structural integrity of small fibers was performed in order to evaluate small fiber neuropathy of peripheral etiology [23-29]. Skin biopsy was not performed on Day 0 if subjects had one performed within the previous 90 days. SPP (SensiLase PAD-IQ system, Väsamed Inc., Eden Prairie, MN) was obtained from the dorsal and plantar surfaces of the foot in the distribution of the dorsalis pedis and lateral plantar arteries, respectively. The dorsal site of probe placement was within 2 cm but not closer than 1 cm from the skin biopsy site. Plantar probe placement was directly below the site of the dorsal probe. Nerve function was tested in two ways. Study site 01 performed NCV testing (Cadwell, Kennewick, WA) and SSR. SSR is a noninvasive method of measuring non-myelinated sympathetic nerve response of the small fiber peroneal nerve branches. The test is performed by placing electrodes on the dorsal and plantar foot. A small electrical stimulation is sent to the electrode on the dorsal foot and the response is measured by the electrode placed on the plantar foot. Amplitude (μV) and time to onset (msec) for both NCV and SSR were recorded. Study site 02 performed NCV utilizing the NC-stat® DPNCheckTM device (Neuromatrix, Waltham, MA). SSR was not performed at study site 02. Subjects were instructed to record their pain scores, utilizing a 1 to 10 visual analog scale (VAS) each day following their morning treatment session. Sites were permitted to use the testing instruments that were part of their specific standard of care.

Treatment period

Subjects in the active group received an active dual field PEMF device (Provant). The device delivers a self-administered, non-thermal, non-ionizing PEMF energy of 27.12MHz pulses lasting 42 microseconds each delivered at a rate of 1000 per second with approximately similar amounts of H and E fields Consistent dosing is ensured through continuous monitoring and regulation by the device. Subjects in the sham group received a sham device which did not deliver PEMF. Subjects were instructed to place a disposable application cover (DAC) over the applicator pad and applying it to the plantar surface of the foot twice daily, once in the morning and once in the evening (8 am ± 2 hours apart) for 60 days starting on Day 1. A telephone interview was performed on Day 14, 28 and 48 to assess adherence with device use and recording of daily pain scores, any changes in concomitant medication use and to record adverse events (Table 1-2).

Final assessment

Subjects returned on Day 61 for a repeat 3 mm punch biopsy of the skin, NCV with or without SSR, and SPP test. This punch biopsy was obtained at a location lateral to the and within 2 cm of the initial biopsy. Compliance with device use was assessed through verification of the usage meter (60 hours total) and documenting the number of unused DACs returned. Compliance was defined as treatment usage of at least 45 hours of the prescribed 60 hours and use of at least 90 DACs.

Statistics

Patient demographic and patient characteristics were summarized descriptively. Skin biopsy, NCV, SSR, and SPP results and daily pain assessments were also summarized descriptively and a probability value was derived from a linear mixed model analysis. A convenience sample was used as the study was not powered for a specific outcome

Results

Figure 1 outlines the subject enrollment, randomization, intent to treat (ITT) and per protocol (PP) subject completion. Two subjects had ABI values outside the ranges set in the exclusion criteria; however as SPP measurements indicated adequate perfusion the subjects were permitted to enter the study. Age, gender, BMI, treated foot ABI and venous insufficiency assessment were similar between the two groups (Table 3). Mean foot thickness was slightly larger in the active group (5.2 cm vs. 4.9 cm).

	Active **n=14**	**Sham** **n=8**
Age (years)	59 ± 9.8	62 ± 7.6
Gender n (%)	8 (57.1%) male 6 (42.9%) female	5 (62.5%) male 3 (37.5%) female
Race n (%)	12 (85.7%) White 2 (14.3%) Hispanic	7 (100%) White
Height (in)*	69.5 ± 5.4	70.9 ± 5.4
Weight (lbs) *	256 ± 5.3	225.9 ± 69.0
BMI (in/lbs) *	36.9 ± 6.2	31.4 ± 8.0
Foot Thickness (cm)	5.22 ± 0.85	4.85 ± 1.01
ABI	1.00 ± 0.17	1.06 ± 0.16

Table 3: Subject demographics in the active and sham groups.

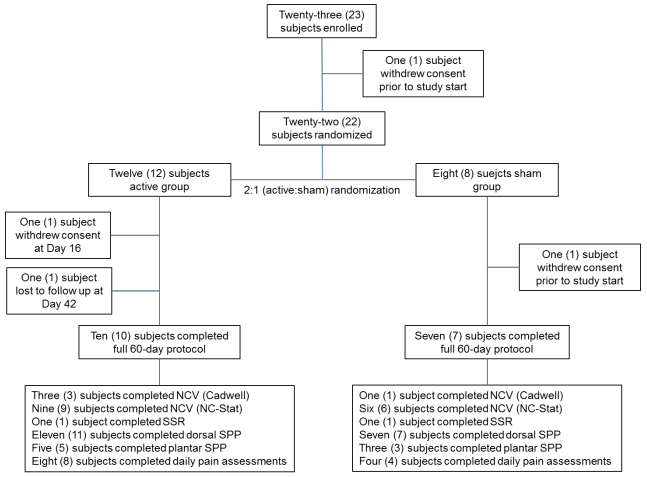

Figure 1: Subject enrollment, Randomization, Intent to treat (ITT) and Per protocol (PP) subject completion.

Objective measures of function

Nerve growth from Day 0 to Day 61 was equivalent with a mean of 0.1 fibers/millimeter intraepidermial nerve fiber density for both groups (active group 12, sham group 7). Decreased latency with increased amplitude was considered indicative of improved nerve function. Four patients (active group 3, sham group 1) had a NCV performed at Day 0 and Day 61 at Study site 01. Assessing both latency and amplitude, a trend towards improved function of the lateral and medial plantar nerves was noted for the active group (lateral plantar nerve mean change from baseline, active vs. sham: onset -0.5 and -0.3, p=0.79; amplitude 0.5 and -0.4, p=0.32 and medial plantar nerve, active vs. sham: onset -0.2 and 0.1, p=0.04; amplitude 0.8 and -0.4, p=0.23). SSR was performed on only one subject each in both groups. NCV at Study Site 02 was performed on 14 subjects (active group 9, sham group 61). A trend toward improved function was seen in the sural nerve for the active group (mean change from baseline, active vs. sham: onset -7.0 and 1.8, p=0.48; amplitude 0.0 and 0.0, p=0.78 (Table 3). For SPP assessment, Study Site 01 enrolled four (4) subjects recording both dorsal and plantar surface measurements for all subjects enrolled. Study Site 02 did not record plantar SPP measurements in eleven (11) of their enrolled subjects. The mean SPP on the dorsal aspect of the foot was associated with a difference favoring the active group (n=11) with a mean change in baseline of 19.6 mmHg (p=0.02) compared to a 17.4mmHg seen for the sham group (n=7). In addition, differences (day 0 to 61) in plantar surface SPP measurements had a positive trend for the active group (29.0 mmHg for the active group (n=5), 3.3 mmHg for the sham group (n=3, p=0.2) (Table 4).

Study Site 01		
NCV		
	Sham Group n=1	**Active Group n=3**
Lateral Plantar Nerve		
Time to onset (msec)	-0.3	-0.5 ± 0.56
Amplitude (mA)	-0.4	0.5 ± 0.58
Medial Plantar Nerve		
Time to onset (msec)	0.1	-0.2 ± 0.06^{+}
Amplitude (mA)	-0.4	0.8 ± 0.6
Peroneal Nerve		
Time to onset (msec)	-1.9^{++}	0.2 ± 0.4
Amplitude (mA)	-0.5	0.4 ± 0.78
Tibial Nerve		
Time to onset (msec)	-0.4	-0.1 ± 0.32
Amplitude (mA)	-3.4	-0.5 ± 3.55
Study Site 2		
NCV		
Sural Nerve	Sham Group n=6	Active Group n=9
Velocity (msec)	1.8 ± 11.11	-7.0 ± 28.25
Amplitude (mA)	0.7 ± 1.03	0.4 ± 1.67

Table 4: Change from baseline in nerve function endpoints.

SPP (mmHg)	**Sham Group n=7**	**Active Group n=11**
Dorsal	-17.4 ± 33.86	19.6 ± 29.92
	Sham Group n=3	Active Group n=5
Plantar	3.3 ± 9.61	29.0 ± 36.64

Table 5: Change from baseline for Skin Perfusion Pressure.

Patient reported outcomes

Mean pain scores decreased by -1.8 in the sham group (n=4) and -0.8 in the active group (n=8). Of note, baseline values were different with a higher mean pain score in the active group (4.6 vs. 2.3). Compliance was over 2-fold higher in the active group (58.3% vs. 28.6%; p=0.6) (Table 5). Despite twice weekly telephone contact with all study subjects, only twelve subjects completed daily written pain assessments. Gabapentin was the most commonly used concomitant medication for treatment of painful DSPN (8/20 subjects; 40%). No changes in the types of routine and as needed analgesic medication were observed. Change in medication consumption was not recorded. No device related adverse effects were reported (Table 6).

	Sham Group	**Active Group**
VAS pain score (mean ± sd)	-1.8 ± 2.26 (n=4)	-0.8 ± 3.27 (n=8)
≥ 90 DAC use	2/8 (25%)	10/13 (76.92%)
≥ 45 hours	2/7 (28.57%)	7/12 (58.33%)

Table 6: Change from baseline for daily visual analogue scale (VAS) scores and subject device compliance.

Discussion

This randomized, double blind, sham controlled study of the safety and efficacy of dual energy PEMF therapy use for the treatment of painful DSPN determined that twice daily use of PEMF in this population is feasible and well-tolerated and may improve nerve function and foot perfusion. DSPN progression parallels diabetic control and may be potentiated by genetic predispositions. The combination of pro-inflammatory cytokines, oxidative stress factors and toxic metabolic by-products associated with prolonged exposures to high levels of glucose and abnormal fat levels result in neuropathy by direct nerve injury and indirect injury via neurovascular damage [30,31]. Life-style alterations and cardiovascular risk reduction may prove useful strategies in retarding disease progression thereby delaying the onset of DPSN-related morbidity and mortality [29]. Other than direct diabetic control medications, pharmacotherapy for DPN is directed towards alterations in symptoms. Such treatment may be helpful in reducing but not eliminating, painful symptoms; however there is a paucity of agents directed towards disease modification.

Preclinical data suggest that PEMF therapy may benefit patients with painful diabetic peripheral neuropathy. Moffett et al. showed that PEMF treatment increased endogenous opioids and opioid receptors 2-3 fold, in vitro studies [21]. Additional in vitro studies supporting an anti-inflammatory response, fibroplasia, angiogenesis, and neuronal sprouting are consistent with the hypothesis that PEMF may retard disease progression through improvement in nerve function and microvasculature circulation [32-34].

A meta-analysis of PEMF support efficacy in relief of traumatic, postoperative, and chronic pain in addition to edema reduction and increased wound healing potential [20]. A randomized controlled trial on the effects of PEMF therapy on nerve growth and function determined that moderate to severe itchy and burning type pain was significantly reduced with active therapy. Change in epidermal nerve fiber density displayed an increasing trend for the active group at 3 months. Nerve function was not objectively assessed [5]. Although the sample size of this pilot study was also small and no change in intraepidermal nerve fiber density was observed, improved nerve function was seen in the nerve distribution where the treatment pad was applied. While distal microcirculation of the hallux has been demonstrated to decrease in healthy subjects and those with Type 2 diabetes and intact skin, blood flow velocity on the dorsal foot significantly increased. This may have occurred due to differences in capillary density or due to a local "steal phenomenon" caused by vasodilation of the more proximal medium sized arterioles [35-37]. In subjects with a diabetic foot ulceration, distal hallux microcirculation increased after 14 sessions of one hour daily PEMF therapy performed over three-week timeframe. Capillary diameter and blood flow velocity significantly increased at one month follow up [7]. These contradictory findings could have been related to the difference in local vasoreactivity and inflammatory changes associated with an active DFU. Larger, properly powered studies are required to confirm these results.

Limitations of this study would be the small size, the number of assessment procedures that were not performed, patient noncompliance with completion of paper based daily pain diary assessments and the potential for continued and as needed oral analgesic use. This trial was designed as a pilot trial to also assess the feasibility of incorporating a variety of assessment procedures. Study center differences in the physiologic objective measures used in their clinical practices contributed to variability; however, such a design was permitted to assist in the feasibility assessments for future trials. The ability of patients to continue utilization of as needed oral analgesics may have resulted in the lack of significant difference seen between the two groups. The two-fold increase in compliance with device use in the active group suggests a non-random difference in the ability of the device to provide alleviation of pain. Future trials may consider the data from this study in determining which endpoint should serve as the basis for the primary endpoint with appropriate power. In addition, studies will need to consider a whether a longer duration of treatment (9-12 months) is needed prior to the final intraepidermal nerve fiber density assessment. Other considerations include alternate biopsy locations such as the distal thigh and distal leg, distinguishing between temporary vasodilation and permanent angiogenesis, more complete nerve conduction velocity testing as this tends to represent improved nerve function in the short term (as compared with nerve biopsy), and utilization of electronic daily pain assessments with reminders to ensure completion and inclusion of specific serum biomarkers shown to be associated with DSPN (34-37).

In conclusion, this pilot study demonstrated potential improvement in nerve function and foot skin perfusion associated with dual field PEMF therapy used for up to 60 days. The potential for improvement in nerve function and microcirculation with PEMF therapy may contribute to the objective of improving quality of life and reducing diabetes-related lower extremity complications. Future, larger randomized controlled trials are necessary to confirm these findings and evaluate the potential longer term benefits on symptoms and neuropathy associated morbidity.

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