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Assessing the Effects of Pulsed Electromagnetic Therapy on Painful Diabetic Distal Symmetric Peripheral Neuropathy: A Double-Blind Randomized Controlled Trial

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Abstract

Background: Significant complications of diabetes include pain and the loss of sensation in peripheral limbs. Pain management of diabetic symmetric peripheral neuropathy (DSPN) remains challenging. This study reports on utilizing pulsed electromagnetic field therapy (PEMF) to reduce pain and improve skin perfusion pressure (SPP) in subjects with DSPN.

Methods: A randomized, sham-controlled, double-blind, clinical trial was conducted on subjects afflicted with foot pain associated with DSPN. Following informed consent, 182 subjects with diabetes and confirmed DSPN were entered into the trial for a period of 18 weeks. Subjects were randomized into active PEMF treatment or nonactive sham and instructed to treat to their feet for 30 minutes, twice daily and report daily pain scores. Some patients in the active arm experienced a transient low field strength notification (LFSN) due to improper pad placement during treatment. Skin perfusion pressure measurements were also collected at two and seven weeks to assess peripheral arterial disease effects via measurement of local microcirculatory flow and blood pressure.

Results: Patients in the active arm who did not receive an LFSN experienced a clinically significant 30% reduction in pain from baseline compared to sham ($P < .05$). Though not statistically significant, SPP in the active group trended toward improvement compared to sham.

Conclusions: Pulsed electromagnetic field therapy appears effective as a nonpharmacological means for reduction of pain associated with diabetic peripheral neuropathy and holds promise for improvement of vascular physiology in microcirculatory dysfunction associated with diabetic peripheral arterial disease.

Keywords

diabetes, diabetic peripheral neuropathy, diabetic symmetric peripheral neuropathy, pain relief, pulsed electromagnetic field therapy

Introduction

In 2023 the U.S. Centers for Disease Control and Prevention (CDC) estimated that 37.3 million people have diabetes, of which 28.7 million are diagnosed and 8.5 million remain undiagnosed.[1] The most common form of diabetes mellitus, type 2 diabetes mellitus, is projected to affect an estimated 366 million people worldwide by 2030.[2] Diabetic neuropathies are the most prominent chronic complications of diabetes,[3] resulting in almost 20% of patients with diabetes developing painful neuropathy.[4,5] A common form of diabetic symmetric peripheral neuropathy (DSPN) is distal symmetric peripheral neuropathy, which accounts for approximately 75% of diabetic neuropathies. Symptoms of

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DSPN are described in terms of increased or decreased sensations resulting from damage of the myelinated and small unmyelinated cutaneous nerve fibers. As the small unmyelinated fibers degenerate, patients experience pain or burning in their feet.[6] With progression, larger myelinated fibers are affected and can be the cause of numbness, tingling, stabbing, and insensate feet. In advanced peripheral diabetic neuropathy, the patient no longer senses pain, developing a loss of the protective sensation, the most common factor to the development of further complications such as diabetic foot ulcerations (DFUs) and Charcot neuroarthropathy.[7-9] Diabetic foot ulceration; a complication that arises in late stages of DSPN, can lead to amputations, increased health economic costs, and death.[10]

Treatment of DSPN remains challenging, and largely relies on custom pharmacotherapy. The maintenance of stable glycemic control has been associated with improvement in neuropathic pain, though it is more effective for patients with type 1 diabetes. Therapeutic intervention for the prevention and treatment of DSPN includes optimized glycemic control, dietary and lifestyle-based counseling, antioxidant-rich nutrition, weight management, moderate exercise, routine foot screening, proper footwear, and avoidance of alcohol and tobacco. Other than tight glycemic control, there are no effective treatments that target the pathophysiology of DSPN. Diabetic symmetric peripheral neuropathy management has focused predominantly on symptomatic pharmaceutical pain control with analgesics and medications such as pregabalin and duloxetine.[3] While tricyclic antidepressants are the most studied agents used for neuropathic pain, the use of such agents has occurred in the absence of regulatory approval from the U.S. Food and Drug Administration (FDA). Duloxetine (Cymbalta) and pregabalin (Lyrica) are medications approved by the FDA specifically for the treatment of painful peripheral diabetic neuropathy. Patients may supplement oral agents with topical therapy. Opioids are generally prescribed for severe, unresponsive pain. Nonpharmaceutical agents such as electrical nerve stimulation,[11,12] acupuncture,[13] electroacupuncture,[14] cognitive behavioral therapy,[15] biofeedback,[16] and physical therapy[17] have some usefulness in treating painful DSPN. The current DSPN treatment relies primarily on custom pharmacotherapy, which often includes addictive agents, such that there continues to be an unmet need for newer, safer therapies for DSPN and its underlying pathology.

Pulsed electromagnetic field (PEMF) therapy is a promising nonpharmacological method to treat pain associated with DSPN and potentially repair the disrupted pathophysiology leading to DSPN.[18-20] The therapy is self-administered at home using a portable medical device that delivers nonionizing pulsed electromagnetic energy using 27.12 MHz pulses lasting 42 microseconds delivered 1000 times per second, settings which have been clinically shown to reduce pain and improve skin perfusion pressure in patients with diabetes.[21,22] Here, we report on a double-blind, sham-controlled, randomized clinical trial conducted to evaluate the utility of PEMF for treatment of DSPN pain. It was hypothesized that PEMF reduces pain associated with DSPN, provides symptomatic relief, as well as enhances skin perfusion pressure.

Methods

Study Design

The trial is registered at the U.S. National Library of Medicine (identifier: NCT03455543, clinicaltrials.gov) where the full study protocol is available. This was a multicenter, double-blind, sham-controlled, randomized pilot trial of the safety, and efficacy of PEMF therapy in subjects with DSPN. Treatment was administered twice daily over a four-month period. The study was conducted at 18 sites in the United States and enrolled 182 subjects. Ethics committee approval was obtained from the Advarra Independent Review Board for each site prior to starting the study. The study was conducted in compliance with the International Standard of Good Clinical Practice (ICH E6-GCP) procedures and the principles of the Declaration of Helsinki (1964).

Study Population

The primary inclusion criteria were documented type 1 or type 2 diabetes mellitus, diabetic peripheral neuropathy confirmed by a score of ≥ 6 on the Toronto Clinical Neuropathy Scoring System (TCNS), daily pain attributed to symmetrical lower extremity diabetic peripheral neuropathy for at least six months prior to screening, stable diabetes treatment for at least three months, and an average lower extremity pain related to DSPN over the preceding 24 hours >4 and <9 based on the 11-point Numerical Pain Rating Scale (NPRS). Potential subjects underwent a Screening Visit (Day 15). Written informed consent for study participation was obtained from all subjects.

Study Procedures

Subjects meeting the eligibility criteria were entered into the 14-day run-in phase of the study. During the run-in, subjects were trained in the use of the electronic patient-reported outcome (ePRO) assessments and were instructed to complete all assessments during the run-in period. Subjects who completed 70% of their ePRO assessments and continued to meet inclusion criteria and none of the exclusion criteria were randomized and enrolled. Randomization was a 1:1 ratio of active PEMF therapy to a sham therapy device. Computer-generated scheme based on a permuted block algorithm was prepared using SAS (Statistical Analysis System; Cary, NC). Randomization was stratified by each site.

Study Devices

The PEMF device used in this study uses a solid-state, fixed-power output radio frequency generator and transmitter designed to operate at the Federal Communication Commission authorized medical device frequency of 27.12 MHz (Regenesis Biomedical Inc., Scottsdale, Arizona). The therapy system generates a treatment consisting of a pulse duration of 42 ± 4 microseconds, repeated every 1000 ± 25 microseconds, resulting in an output duty cycle of 4.2%, and requiring an average RF forward power level of <3 Watts. The device was equipped with two pads that fired asynchronously, giving the ability to treat both feet concurrently.

Outcome Measurements

Pain Assessment

Subjects used a validated 11-point (0-10) Numeric Pain Rating Scale (NPRS) to report average pain score (PI) over the preceding 24-hours using an ePRO diary. For analgesic consumption, subjects reported the number of pills they had taken over the last 24 hours (both over the counter and prescription medication).

Skin Perfusion Pressure

Subjects were tested for perfusion pressure (SPP) using the Sensilase PAD-IQ (Vasamed, Prairie, MN) device, which measures mm Hg, using a laser Doppler sensor to assess capillary perfusion. Subjects were measured as follows, first, in a supine position the laser sensor assembly (LSA) was inserted into the LSA placement guide. The optical sensor window was oriented toward the skin of the foot. A cuff was positioned such that the LSA is centered, following an increase in pressure to the cuff to pressure necessary to occlude blood flow. The PAD-IQ devices then released the pressure at a controlled rate, measuring the point at which perfusion returns, calculating the SPP. Measurements were taken on the dorsal aspect of each foot and on the plantar aspect of each foot at baseline, Months 2 and 4.

Safety

Safety was monitored through the review of adverse events, including serious adverse events. Adverse events were assessed at enrollment, interim visits, and the Month 4 visit.

Low Field Strength Notification

In 34 active subjects, a Low Field Strength Notification (LFSN) occurred on the treatment device. After the study concluded, and device data were unblinded, the source of the error was identified. A root cause analysis of the LFSN uncovered an issue with the applicator cables. When the applicator cables were intertwined with each other, there was a noted decrease in field strength which made it difficult for the device to maintain the full effective range. The measured field strength declined on average from 26 A/m to 18 A/m; levels that are consistently lower than the expected average field strength levels. It is reasonable to assume that subjects with devices with one or more LFSN received a lower average field strength when compared to subjects with devices that did not exhibit any LFSN. Since the dosage of the device to subjects who received LFSN errors is unknown, they were removed from some analyses, as explained below. After study conclusion, applicator cable improvements have been implemented that address the LFSN errors that occurred.

Statistical Methods

A total of 182 (81 active and 83 sham) subjects underwent at least one treatment and one follow-up contact that included collection of adverse events. Analysis of the primary endpoint and safety was performed on this population (intention to treat, ITT). The per protocol (PP) population included 137 subjects (68 active and 69 sham) and consisted of subjects that completed the four-month treatment period and were ≥70% compliant with study device usage. For the post-hoc pain analyses, any subject receiving a LFSN error was removed to control for potential nocebo effects and potential lower dosing on reported pain scores related to the LFSN, referred to herein as the error-free population. The ITT error-free population included 46 active and 83 sham subjects. Statistics calculated for skin perfusion pressure included all subjects in the ITT population (N = 182).

All statistics were conducted in *R* v4.1.0 and Intellectus Statistics.[23,24] Summary statistics were generated for outcome measures and potentially confounding variables including use of analgesics and opioids. Change in pain was analyzed in two ways, first as an absolute two-point reduction in pain (primary endpoint), and second as a 30% reduction in pain over the course of treatment. The two-point reduction in pain was correlated with the 30% reduction ($P < .001$, $r = .99$) but had a lower sample size and was thus removed from further analyses. Individuals that reported >30% decrease in pain scores were designated as experiencing pain relief and responding to treatment. Pain response analyses were conducted at both the full time series of 18 weeks and at eight weeks, the typical length of clinical trials. For each of the pain outcome measures, we conducted a Wilcoxon Rank Test with Bonferroni correction to identify whether the error-free active treatment group was significantly different from the sham group.

For outcome measures that were not correlated (i.e., $P > .05$), a repeated measures multivariate analysis of variance (MANOVA) with two within-subject factors was conducted to determine whether significant differences exist among the time points for these outcome measures.

Next, we conducted an analysis of variance (ANOVA) on a linear model (Pain ~ Week 8 × Week 0) to identify whether

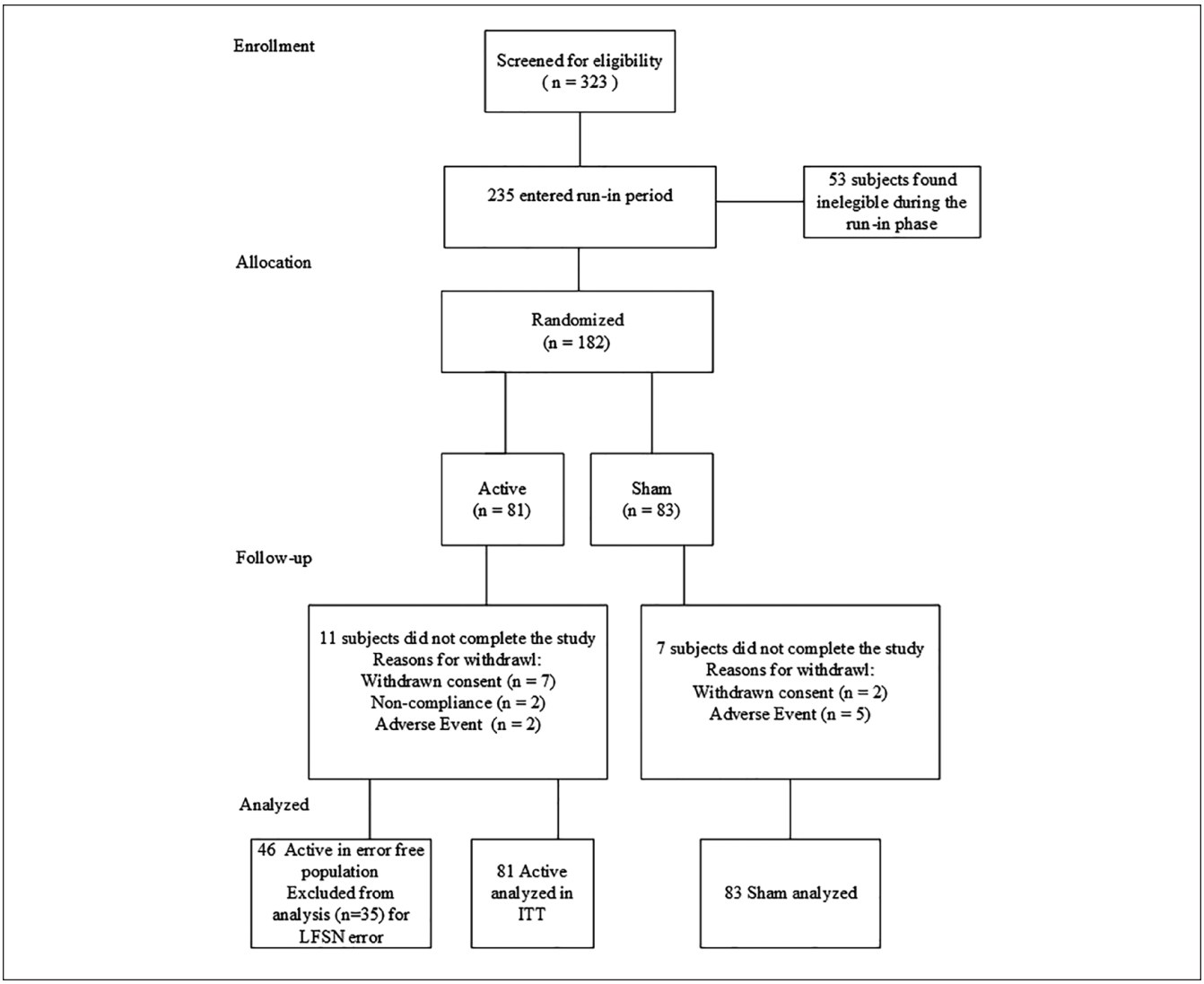

Figure 1. Subject screening, Enrollment, Randomization, ITT, and error-free subject completion (those with LFSN).
Abbreviations: ITT, intent to treat; LFSN, low field strength notification.

the starting pain score determined whether or not a subject experienced relief after eight weeks of treatment. Pain was categorical yes or no of experiencing at least 30% reduction in pain, Week 0 was the subject's pain scores at the start of the trial and Week 8 was the pain score at Week 8 of the trial. We conducted an ANOVA on a linear mixed model to examine the effect that each of the outcome measures had a significant effect on pain reduction. To identify the timepoint when subjects experienced a drop in pain, we identified the inflection point for the full trial (18 weeks) and at eight weeks.

Results

In total, 323 subjects were screened, and of those screened, 235 entered into the 14-day run-in period. Fifty-three subjects were found to be ineligible during the run-in phase of the study, leaving 182 subjects who were enrolled and received at least one treatment (ITT population, Figure 1). One hundred sixty-four subjects completed the 120-day treatment protocol, with 137 subjects adhering to ≥70% compliance with study device use. Eighteen subjects withdrew early; reasons for early termination include: withdrawn consent (9), noncompliance with study protocol (2), adverse event (AE) deemed possibly related to study device (3), and AE unrelated study device (2), and significant adverse event (SAE) unrelated to study device use (2).

Demographics

Demographics between groups were generally similar and nonsignificant (Table 1), with the exception of a higher body mass index (BMI) in the Active group compared to subjects

Table 1. Subject Demographics in the Active and Sham Groups.

Characteristic	Parameter	Active (n = 92)	Sham (n = 90)	*P* value
Age (y)	Mean ± SD	62.27 ± 10.21	62.17 ± 9.33	.94
Gender, n (%)	Male	42 (45.7%)	42 (46.7%)	1
	Female	50 (54.3%)	48 (53.3%)	
Race, n (%)	White	74 (80.4%)	73 (81.1%)	.77
	Black	15 (16.3%)	14 (15.6%)	
	Asian	3 (3.3%)	1 (1.1%)	
	American Indian or Alaska Native	0 (0%)	1 (1.1%)	
Ethnicity, n (%)	Multirace	0 (0%)	1 (1.1%)	.54
	Hispanic or Latino	12 (13.0%)	15 (16.7%)	
	Not Hispanic or Latino	80 (87.0%)	75 (83.3%)	
Height (inches)	Mean ± SD	66.40 ±3.96	66.58 ± 3.82	.76
Weight (lbs.)	Mean ± SD	219.44 ± 44.29	207.11 ± 42.42	.06
BMI (kg/m^2)	Mean ± SD	34.97 ± 6.49	32.84 ± 6.26	.03
Foot thickness—left (cm)	Mean ± SD	6.06 ± 1.25	5.84 ± 1.09	.22
Foot thickness—right (cm)	Mean ± SD	6.12 ± 1.28	5.88 ± 1.08	.17
Venous insufficiency—left	C0	49 (53.3%)	53 (58.9%)	.78
	C1	17 (18.5%)	12 (13.3%)	
	C2	13 (14.1%)	11 (12.2%)	
	C3	7 (7.6%)	9 (10.0%)	
	C4	6 (6.5%)	4 (4.4%)	
	C5	0 (0.0%)	1 (1.1%)	
Venous insufficiency—right	C0	49 (53.3%)	53 (58.9%)	.94
	C1	17 (18.5%)	12 (13.3%)	
	C2	12 (13.0%)	11 (12.2%)	
	C3	8 (8.7%)	9 (10.0%)	
	C4	5 (5.4%)	4 (4.4%)	
	C5	1 (1.1%)	1 (1.1%)	
Diabetes type	Type I	3 (3.3%)	7 (7.8%)	.56
	Type II	89 (96.7%)	83 (92.2%)	
HbA1c (mmol/mol)	Mean ± SD	6.86 ± 1.13	7.13 ± 1.29	.13
Toronto Clinical Neuropathy Score (TCNS)	Mean ± SD	11.48 ± 3.02	11.23 ± 2.69	.56

Abbreviations: SD, standard deviation; BMI, body mass index; HbA1c, hemoglobin A1C.

in the Sham group ($P = .0252$); however, the standard deviation is overlapping in measurements. The age of subjects was similar for the Active and Sham groups. The mean age of subjects was 62.3 years for the Active group and 62.2 years for the Sham group. There were approximately an equal number of men and women in both the Active and Sham groups.

Analysis of the primary endpoint was performed on the ITT error-free population (46 active and 83 sham); safety was performed on the ITT population. The per protocol (PP) population included 137 subjects (68 active and 69 sham) and comprised subjects that completed the four-month treatment period and were ≥70% compliant with study device usage. The error-free PP population included 33 subjects.

Pain Reduction

When assessing the number of subjects who received at least 30% pain relief, subjects in the ITT active, error-free group reported significantly more pain relief compared to subjects in the sham group ($P < .01$, Figure 2). We also analyzed the responsiveness to PEMF treatment in both the PP and ITT active, error-free population and sham populations using the

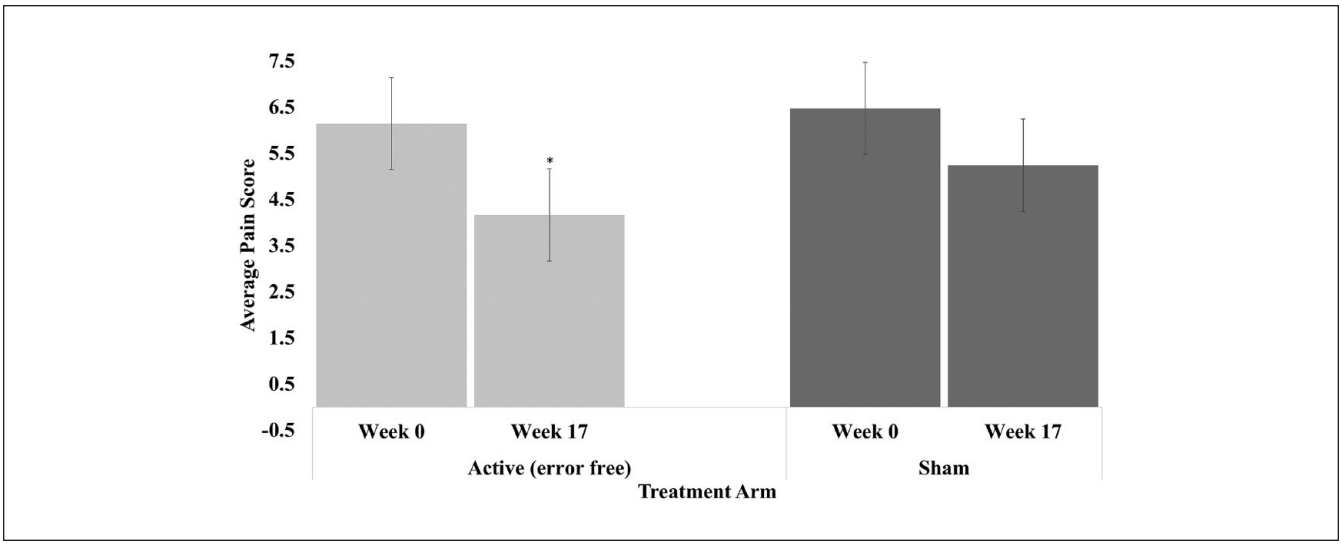

Figure 2. Average Pain scores over time for ITT Active error-free population and Sham population over course of trial.
Abbreviation: ITT, intent to treat.
Average change was significant in the Active error-free population compared to Sham (*$P < .001$). Timepoints are at baseline and end of study (Week 17).

at least 30% reduction in pain and a two-point reduction in pain as separate criteria, where patients meeting these thresholds in each group were included. In the ITT active, error-free population we saw 48% (at least 30% reduction criteria) and 43% (two-point reduction criteria) of subjects respond to treatment compared to 28% and 24% of sham subjects, respectively (Table 2, Figure 3).

The use of analgesics and/or narcotics did not significantly contribute to pain reduction ($P > .05$). The data indicated a change in inflection in pain scores at Week 3.5 when analyzed to eight-weeks, and at Week 9 when the full trial data set was examined (18 weeks).

Skin Perfusion Pressure

There was no significant change in skin perfusion pressure between the ITT active and sham groups (Mann-Whitney Test, $U = 2410$, $z = -0.43$, $P = .670$); however, subjects in the active group trended toward higher values in both feet, whereas subjects in the sham population trended lower (Figure 4).

Discussion

This double-blind, sham-controlled, randomized trial of PEMF therapy for treatment of pain relief in DSPN subjects determined that twice-daily use of PEMF contributes to a significant reduction in pain over time. In this study, 30% of subjects in the ITT active, no error therapy group, experienced 50% or greater pain relief. In the PP active, no error therapy group 36% of patients experienced the same amount of pain relief. Pregabalin, an FDA approved drug for treatment of DSPN, has shown favorable outcomes in many studies with 39% to 57% of patients experiencing a 50% reduction in pain compared to 22% of placebo.[25,26] A review of the second line of therapy, gabapentin, has shown 38% of subjects with DPN experienced 50% reduction in pain relief compared to 23% given placebo.[25] While our results do not reach the same efficacy as the pharmacological options, PEMF is a safe form of therapy with minimal side effects and no known drug interactions. Pulsed electromagnetic field therapy has emerged as a treatment of diabetic complications[22] and has shown pain reduction,[18] and improved wound healing[27-29] in both clinical and preclinical studies. Additionally, PEMF has shown clinical improvement in other pain conditions[21,30,31] (eg, knee osteoarthritis, plantar fasciitis, failed back), increasing the body of evidence suggesting PEMF is an efficacious clinical tool for pain management.

The perception of pain can be largely subjective; there warrants some caution in using pain as pure endpoint measurement when nocebo and placebo effects may alter patient perceptions.[32] In this study, a nocebo effect is hypothesized to have occurred when subjects experienced a low field strength notification (LFSN) prior to treatment. The error may have changed the subjects' expectation of pain relief[32]; however, there is evidence of a positive physiological change. The trend-to-improvement, though not significant, in skin perfusion pressure calculated over the ITT population indicates that despite differing pain outcomes in the ITT and error-free population, physiological improvements were observed in subjects who received the LFSN. The improvements in the objective SPP measurements, support our hypothesis of a nocebo effect in the active group receiving

Table 2. Subjects Experiencing Pain Relief Expressed as Change From Baseline (Percentages) and Two-Point Reduction by Analysis Group and Treatment Type.

Percent pain relief (inclusive)	ITT active, error free	ITT sham	PP active, error free	PP sham
≤9%	13 (28%)	36 (40%)	9 (27%)	29 (42%)
10%	5 (11%)	20 (22%)	3 (9%)	15 (22%)
20%	6 (13%)	9 (10%)	3 (9%)	3 (4%)
30%	5 (11%)	6 (7%)	4 (12%)	6 (9%)
40%	3 (7%)	4 (4%)	2 (6%)	4 (6%)
50% +	14 (30%)	15 (17%)	12 (36%)	12 (17%)
Two-point reduction	20 (43%)	22 (24%)	17 (52%)	19 (28%)
Total subjects	46	90	33	69

Abbreviations: ITT, intention to treat; PP, per protocol.

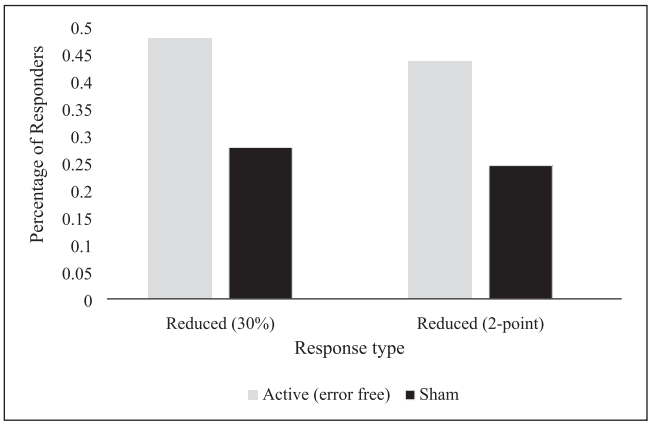

Figure 3. Percentage of ITT Active error-free and Sham population responding to PEMF therapy using at least 30% reduction in pain criteria and an absolute two-point reduction in pain criteria.
Abbreviation: ITT, intent to treat; PEMF, pulsed electromagnetic field therapy.

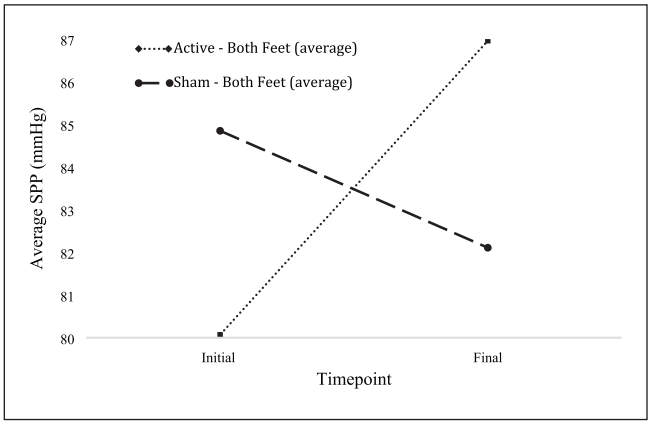

Figure 4. Change in averaged skin perfusion pressure (SPP) (mm Hg) over time measured on the plantar aspect of both feet at initial and at final (Month 4) timepoints in Active ITT and Sham populations.
Abbreviations: ITT, intent to treat; SPP, skin perfusion pressure.

the LFSN. In the error-free population, application of PEMF significantly reduced pain in 50% of the subject population, independent of the medications prescribed to treat DSPN pain. Of the total 46 subjects in the error-free population, 85% experienced some additional relief with PEMF therapy compared to only 25% of the Sham population (Figure 4). Any change in the sham population is presumed to be due to the placebo effect. Application of PEMF is a safe, nonaddictive, drug-free option to improve pain in patients suffering from DSPN.

Skin perfusion pressure is a noninvasive technique to measure microcirculatory blood pressure. As a diagnostic method, SPP is an objective indicator of healing potential, and an assessment of the severity of peripheral arterial disease. Skin perfusion values offer guidelines that can predict the healing potential of ulceration—a common occurrence in DSPN patients with limited sensitivity. Studies have shown a correlation between SPP values and wound healing, with values >40 mm Hg used as a cutoff for clinical decision making.[33,34] Clinical interventions to improve blood flow and SPP include pentoxifylline, clopidogrel, and cilostazol.[35,36] These drugs work differently, interacting with vasculature and red blood cells, by improving malleability of the red blood cells, inhibiting platelet aggregation, dilating arteries, and relaxing blood vessels. Our results in the active population show a trend toward improvement in SPP, whereas in the sham population, the trend is moving toward deterioration/worsening. Our data suggest an alternative to pharmacotherapy to improve SPP in DSPN patients.

The laser doppler measurements of SPP are taken at a depth of 1 to 2 mm from the skin surface, and the PEMF utilized in this study shows sustained field strengths at 5 cm above the center of the therapy pad, and therefore capable of reaching the same microvasculature measured. Though not statistically significant, the improvements in SPP values in DSPN subjects may improve wound healing. In a population susceptible to diabetic foot ulcers (DFU), this result is promising for improving circulatory functionality and wound healing, should a

patient develop a DFU. Additional studies are needed to confirm the positive effects of PEMF on SPP in a larger patient population.

Conclusions

Pulsed electromagnetic therapy appears effective as a nonpharmacologic means to reduce pain associated with diabetic peripheral neuropathy. Pulsed electromagnetic field therapy also appears to have some modulatory affect enhancing blood flow in affected tissue. Pulsed electromagnetic field therapy appears to be a potential nonpharmacological therapeutic with efficacy as a primary therapy, or as an adjunctive therapy, reducing pharmacologic burden and risk of addiction in patients with symptomatic pain in DSPN. Pulsed electromagnetic field therapy holds promise for improvement of vascular physiology in microcirculatory dysfunction associated with Diabetic PAD and warrants additional investigation as to underlying mechanisms and further clinical translation.

Abbreviations

AE, adverse event; ANOVA, analysis of variance; CDC, Center for Disease Control; DFU, diabetic foot ulcer; DSPN, diabetic symmetric peripheral neuropathy; ePRO, electronic patient-reported outcome; FDA, Food and Drug Administration; ITT, intention to treat; LFSN, low field strength notification; LSA, laser sensor assembly; MANOVA, multivariate analysis of variance; NPRS, numerical pain rating scale; PAD, peripheral arterial disease; PEMF, pulsed electromagnetic field; PI, pain score; PP, per protocol; SAE, Serious adverse event; SPP, skin perfusion pressure.

Declaration of Conflicting Interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Erica E. Tassone is a full-time employee of Regenesis Biomedical Inc., Jeffrey C. Page is a member of the medical advisory board of Regenesis Biomedical Inc., Marvin J. Slepian is a member of the board of directors of Regenesis Biomedical Inc.

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