ORIGINAL ARTICLE

Pulsed Electromagnetic Fields to Reduce Diabetic Neuropathic Pain and Stimulate Neuronal Repair: A Randomized Controlled Trial

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ABSTRACT. Weintraub MI, Herrmann DN, Smith AG, Backonja MM, Cole SP. Pulsed electromagnetic fields to reduce diabetic neuropathic pain and stimulate neuronal repair: a randomized controlled trial. Arch Phys Med Rehabil 2009;90:1102-9.

Objective: To determine whether repetitive and cumulative exposure to low-frequency pulsed electromagnetic fields (PEMF) targeting painful feet can reduce neuropathic pain (NP), influence sleep in symptomatic diabetic peripheral neuropathy (DPN), and influence nerve regeneration.

Design: Randomized, double-blind, placebo-controlled parallel study.

Setting: Sixteen academic and clinical sites in 13 states.

Participants: Subjects (N=225) with DPN stage II or III were randomly assigned to use identical devices generating PEMF or sham (placebo) 2 h/d to feet for 3 months.

Interventions: Nerve conduction testing was performed serially.

Main Outcome Measures: Pain reduction scores using a visual analog scale (VAS), the Neuropathy Pain Scale (NPS), and the Patient's Global Impression of Change (PGIC). A subset of subjects underwent serial 3-mm punch skin biopsies from 3 standard lower limb sites for epidermal nerve fiber density (ENFD) quantification.

Results: Subjects (N=225) were randomized with a dropout rate of 13.8%. There was a trend toward reductions in DPN symptoms on the PGIC, favoring the PEMF group (44% vs 31%; P=.04). There were no significant differences between PEMF and sham groups in the NP intensity on NPS or VAS. Twenty-seven subjects completed serial biopsies. Twenty-nine percent of PEMF subjects had an increase in distal leg ENFD of at least 0.5 SDs, while none did in the sham group (P=.04). Increases in distal thigh ENFD were significantly correlated with decreases in pain scores.

Conclusions: PEMF at this dosimetry was noneffective in reducing NP. However neurobiological effects on ENFD, PGIC and reduced itching scores suggest future studies are indicated with higher dosimetry (3000–5000 G), longer duration of exposure, and larger biopsy cohort.

Key Words: Electromagnetic fields; Rehabilitation.

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REPETITIVE TRANSCRANIAL magnetic stimulation at the prefrontal,[1] motor,[2] and somatosensory cortex[3] is emerging as a promising alternative therapy for disabling and refractory NP. Short-term analgesic and antinociceptive effects have also been achieved with direct stimulation of the spinal cord[4] and lumbar nerve roots.[5] Both low-frequency and high-frequency magnetic stimulation can influence thermal and pain thresholds in both normative and symptomatic subjects for a short time, yet the specific mechanisms of action are yet to be determined.[6-10] Despite these preliminary data with small cohorts receiving isolated treatments only at academic clinics, there has been no information regarding its efficacy in painful DPN, which is one of the most common causes of NP. It has been estimated that 40% to 50% may experience NP.[11] DPN begins insidiously in the feet with preferential involvement of unmyelinated C fibers and small myelinated A delta fibers.[12] From a pathophysiological standpoint, DPN symptoms are believed secondary to ectopic firing of nociceptive afferent axons that are undergoing degeneration, with dysregulated expression of sodium, calcium, and potassium channels.[13-15] Skin biopsies reveal prominent cutaneous denervation with length-dependent reductions in ENFD.[16,17] The mechanisms of DPN and NP are considered multifactorial.[18] Impaired production of neurotrophic factors (NGF, IGF-I, IGF-II, fibroblast growth factor, and so forth),[19-21] impaired Schwann cells,[19,22] macrophage dysfunction,[19,23] microangiopathy with ischemia

List of Abbreviations

DPN	diabetic peripheral neuropathy
ENFD	epidermal nerve fiber density
HbA1C	glycosylated hemoglobin
IGF-I	insulin-like growth factor I
IGF-II	insulin-like growth factor II
NGF	nerve growth factor
NP	neuropathic pain
NPS	Neuropathy Pain Scale
PEMF	pulsed electromagnetic fields
PGIC	Patient's Global Impression of Change
VAS	visual analog scale
VEGF	vascular endothelial growth factor

and reduced VEGF,[19,24] impaired voltage-gated channels (sodium, potassium, calcium),[13,15,25] protein kinase C dysregulation,[19,26] and oxidative stress[19,27,28] are believed to be contributory. Data from cell culture, animal, and human studies suggest that exogenous application of weak, nonthermal electromagnetic fields upregulates NGF, IGF-I, IGF-II, fibroblast growth product, and VEGF[29-31]; reorients Schwann cells[32]; enhances macrophage activity[33] and endoneurial blood flow[34]; reduces nociceptive afferent signal transduction[35-38]; reduces free radicals[37,39] and oxidative stress[33,40]; and promotes neurite outgrowth.[35,41] Thus, magnetic stimulation may be an appropriate noninvasive intervention that could reduce DPN symptoms and produce disease modification.[35,37]

METHODS

Enrollment Criteria

The design and conduct of the randomized controlled trial is described in the accompanying consort flow diagram (fig 1). Subjects from 18 to 87 years of age with painful DPN (Dyck stage II or III)[38] with moderate-severe constant pain of 4 or higher on a 0 to 10 VAS, with a duration of at least 6 months, were recruited at 16 investigative sites in 13 states within the United States (appendix 1) between August 2005 and March 2007. Pregnant women and subjects with mechanical insulin pumps or cardiac pacemakers were excluded. Subjects could remain on their stable drug medications for diabetes and pain relief, but no new analgesics or dosing increases were permitted during the trial. Subjects were enrolled only if they were on a stable analgesic regimen. Before randomization, subjects were instructed on how to tabulate VAS (0–10) pain scores (3 times a day) and a sleep interference score (VAS 0–10, once daily). All participants provided written informed consent. Two university centers performed skin-punch biopsies at random-

ization and at conclusion of the study that were shipped to the University of Rochester for immunohistochemistry and measurement of ENFD.

Randomization

Demographic data (age, height, weight, sex, glycosylated hemoglobin [HbA1C], family history, duration of diabetes, concomitant medications) were collected for each enrolled subject. After entry and baseline quantification of pain and sleep interruption scores, eligible patients were randomized (1:1 via computer assignment) to receive an active coded magnetized or a sham device, identical in all characteristics except for the demagnetization procedure. Subjects agreed to use the device a maximum of 2 hours a day in divided sessions of 10 to 30 minutes for 3 months. Subjects recorded daily VAS pain and sleep scores; other outcome measures (see below) were evaluated at monthly study visits. All subjects agreed not to break the blinding of the devices. A consecutive subset of patients from 2 university sites volunteered to participate in an ENFD exploratory substudy. Three-millimeter punch skin biopsies were harvested from the proximal and distal lateral thigh, and the distal leg at baseline and after 3 months of PEMF or sham exposure. The skin biopsies were fixed, cryoprotected, sectioned, and immunostained with polyclonal antibodies to the panaxonal marker, protein gene product 9.5, according to previously published methods.[42,43] A single blind observer assessed both the linear density (fibers/mm) of nerve fibers crossing the dermal-epidermal junction ENFD (crossings) and the total linear density including intraepidermal fragments ENFD (total) from three to five 50-μM thick sections selected at random from each biopsy specimen, using previously published techniques.[44,45]
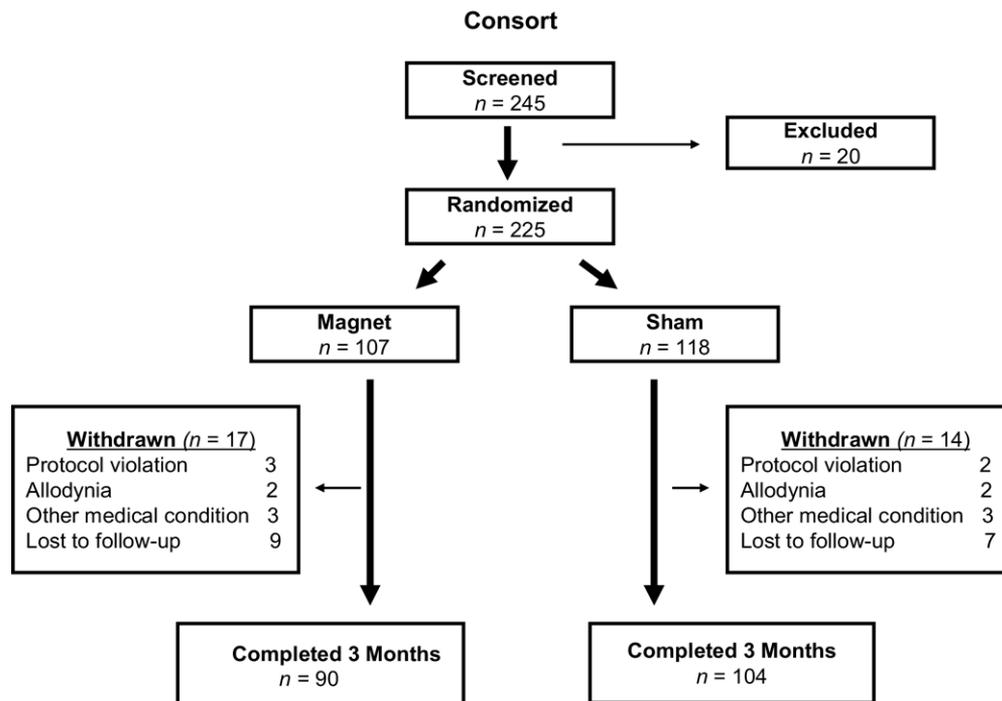
Consort

Fig 1. The CONSORT diagram revealing enrollment and outcomes. A total of 245 subjects were screened, and 225 were randomized and enrolled. A 13.8% dropout occurred (31/225) with no safety issues.
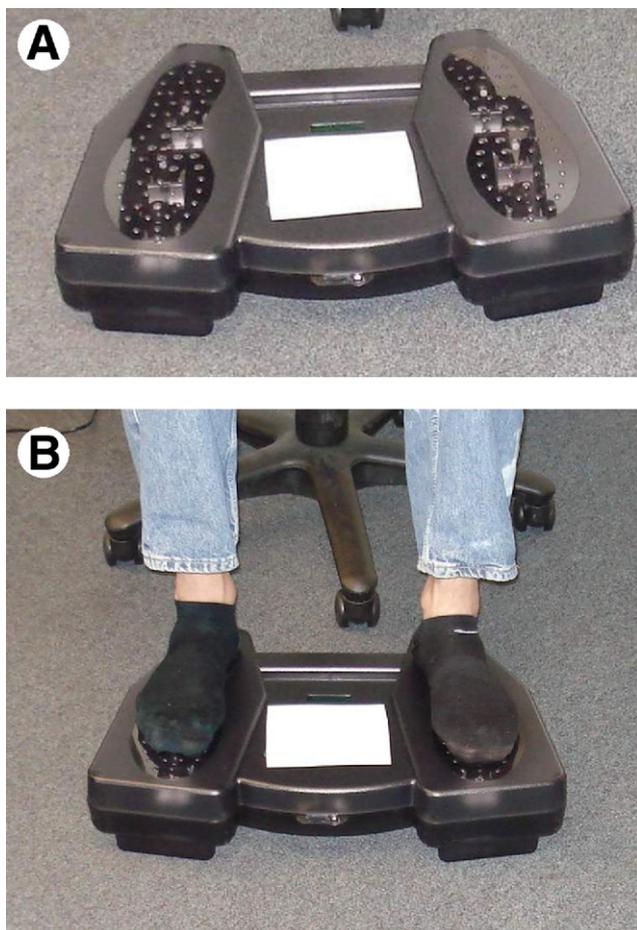
Fig 2. Device: Body Energizer.[a] (A), PEMF and/or identical sham demagnetized device. (B), Subject with feet in place.

Device

This device (fig 2) uses 6 individual (1800-G) magnetic sphere units, 3 under each foot, that are driven individually by a 6-V DC motor. A speed control circuit allows a range of 500 to 1500 revolutions per minute. The magnetic spheres turn on one axis generating magnetic lines of force (flux), and simultaneously, turn on a second axis perpendicular to the first axis (biaxial), causing the moving flux lines to cut across tissues at varying periodic angles, inducing varying intensities of force and polarity changes, resulting in static and time-varying magnetic fields. Precise placement on the foot plates with socks allows penetration of the magnetic fields up to 5 feet as measured by an ENF meter[b] (model UHS). There is exponential decay of field strength with distance from magnetic source (310,000 mG). Supersaturation of the target area from every angle at 25 times a second at maximum 1500 revolutions per minute is achieved. The barium ferrite-nylon bonded spheres do not induce any discernable sensory effects on the feet to suggest device activity.

Outcome Measures

Pain is a complex experience, and none of the existing pain scales appears to be ideal for all situations. Thus, we chose a priori to employ 3 of the most commonly used validated NP measures as outcomes for the trial.

Primary outcome. The primary outcome was a VAS (ranging from 0, no pain to 10, worst possible pain),[38] 3 times daily at the same time to represent a mean daily pain level.

Secondary outcomes. NPS assessed 10 pain descriptors collected at baseline and the end of the study.[43] NPS composite (NPS 10) scores range from 0 to 100.

PGIC[46] required subjects to select 1 of 7 options describing response to treatment, ranging from "very much improved" to "very much worse."

VAS measure of sleep disruption[38] secondary to pain was collected once on arising each morning.

Other secondary outcomes compared baseline and 12-week values of the neurologic examination (sensory, motor, reflex functions). Standardized nerve conduction velocities and amplitudes of common peroneal nerve (recording from the extensor digitorum brevis muscle) and sural nerves were monitored at baseline and the end of the study for abnormalities consistent with distal polyneuropathy. At the end of the study, both patients and investigators were asked for their perception of device activity.

Statistical Analyses

Based on prior pilot VAS pain data,[38] a sample size of 200 patients was calculated to yield a power of 80% to detect a 25% superiority of PEMF over sham placebo with alpha equal to 0.05 and beta equal to 0.20. We allowed for a dropout rate of 20% of subjects enrolled. For the NPS, 10 composite scores (range, 0–100) were used. In addition, 2 NPS items most salient to C-fiber involvement, itchy pain and burning pain (ranges, 0–10), were analyzed separately. ENFD change scores were computed by subtracting the baseline value from the 3-month value; a positive change score indicated an increase in ENFD. Change scores as continuous measures were used for correlation analyses. To assess treatment effects on ENFD, 3 categories were constructed based on a 0.5 SD of the baseline value: (1) >0.5 SD change (indicating increase in ENFD), (2) −0.5 to 0.5 (no or little change) and (3) > −0.5 SD change (decrease). The 0.5 SD criterion was chosen to be sensitive to the different levels of variability of the ENFD measures. Associations between treatment and ENFD groups were assessed with chi-square tests.

Two (PEMF, sham) $\times$ 2 (baseline to month 3) repeated-measures analyses of variance were used to assess change in pain scores and ENFD values over the course of the study. A statistically significant treatment group $\times$ time interaction indicated greater change from baseline to the end of month 3 for 1 of the treatment groups. Independent sample t tests were used to test for possible baseline differences in mean scores and for the PGIC at 3 months.

For the a priori statistical tests of the primary outcome measure, the level of significance was set at $P < .05$. For the 3 secondary outcome measures, a Bonferroni correction adjusted the statistical significance level to .017. For the Pearson product moment correlation analyses between ENFD values and pain measures, the researchers controlled for familywise error rate using a sequential Bonferroni approach: significance was set at $P < .008$. All tests were 2-sided. All analyses were conducted in an intent-to-treat manner (expectation maximization method). The Statistical Package for the Social Sciences (version 15.0[c]) was used to analyze the data.

RESULTS

The flow of patients through the clinical trial is depicted in figure 1 (CONSORT diagram). Of the 245 subjects enrolled in this study, 20 cases were initially excluded because of a low

Table 1: Baseline Demographics and Clinical Characteristics of the Enrolled Patients

Characteristic	PEMF Group (n=90)	Sham Group (n=104)
Age (y)		
Mean	61.1±10.4	60.6±12.4
Range	33–87	21–83
Weight (lb)	217.9±55.6	215.1±54.6
Height (in)	66.6±4.54	67.4±4.42
Female (%)	56.7	55.8
Years since onset of diabetes	3.9±3.0	4.0±3.0
HbA1c	7.5±1.8	7.4±1.8
Subjects with abnormal nerve conduction (%)	87.7	89.9

NOTE. Values are mean ± SD unless otherwise noted.

baseline score. Of the 225 patients randomized, there was a dropout of 31 subjects (13.8%). These included 5 because of protocol violations, 6 from diabetic complications, 16 lost to follow-up, and 4 who did not complete the study because of allodynia. Three of these 4 cases had significant premorbid burning feet syndrome with pressure allodynia. Of the 107 patients allocated to the magnet group, 90 (84.1%) completed the 3-month study, whereas 104 of the 118 allocated to the sham group (88.1%) completed the study. The dropout rate and withdrawal pattern were similar for both groups. Baseline demographics (table 1) were similar for both groups. Women represented 56.7% of the PEMF group and 55.8% of the sham group. Mean ± SD ages were 63.6±8.6 years and 63.5±9.5 years for the PEMF and sham groups, respectively. HbA1c data were similar for both groups at 3 months. There were also no changes in motor or sensory conductions or the sensory/motor neurologic examination at 3 months. Seventy-four percent of patients who completed the study took at least 1 analgesic medication for pain, and 47% took at least 2 agents. There were no group differences in number of antiepileptic drugs, narcotics, tricyclics, selective serotonin reuptake inhibitors, or nonsteroidal anti-inflammatory drug medications taken by patients.

For the biopsy cohort (CONSORT diagram) (fig 3), of the 37 subjects enrolled in the study, 10 (27.0%) were lost to follow-up (3 magnet, 7 sham). Of the remaining 27 cases, 14 had received active magnets, and 13 had received sham devices. Women represented 64.3% of the PEMF group and 38.5% of the sham group. Mean ages were 63.6 and 63.5 years for the PEMF and sham groups, respectively.

Primary and Secondary Outcomes

Results for study outcomes are presented in table 2. There were no statistically significant group differences in baseline pain measures. For PGIC at 3 months, 43.7% of PEMF and 30.6% of sham group subjects reported very much or much improvement (P=.04). This result was considered a nonsignificant trend. Group differences from baseline to 3 months were not significant for VAS (P=.96), NPS 10 (P=.58), sleep scores (P=.49), or electrodiagnostic studies. Analyses controlling for baseline HbA1c (PEMF mean,7.5; sham mean,7.4) and whether subjects were taking insulin (10% PEMF; 28% sham) also did not reveal significant group differences. However, for subjects with moderate to severe itchy pain, there was a 53.7% reduction in mean itchy pain scores for the PEMF group from baseline to 3 months, whereas there was a 33.8% reduction for the sham group (P=.048). Subjects who reported higher levels of itching also reported higher levels of burning at baseline (r=.32; P<.001) and at 3 months (r=.33; P<.001).

Correlations Between Pain Measures

At baseline, the correlations between NPS 10 (only the total composite score was analyzed) and VAS was significant
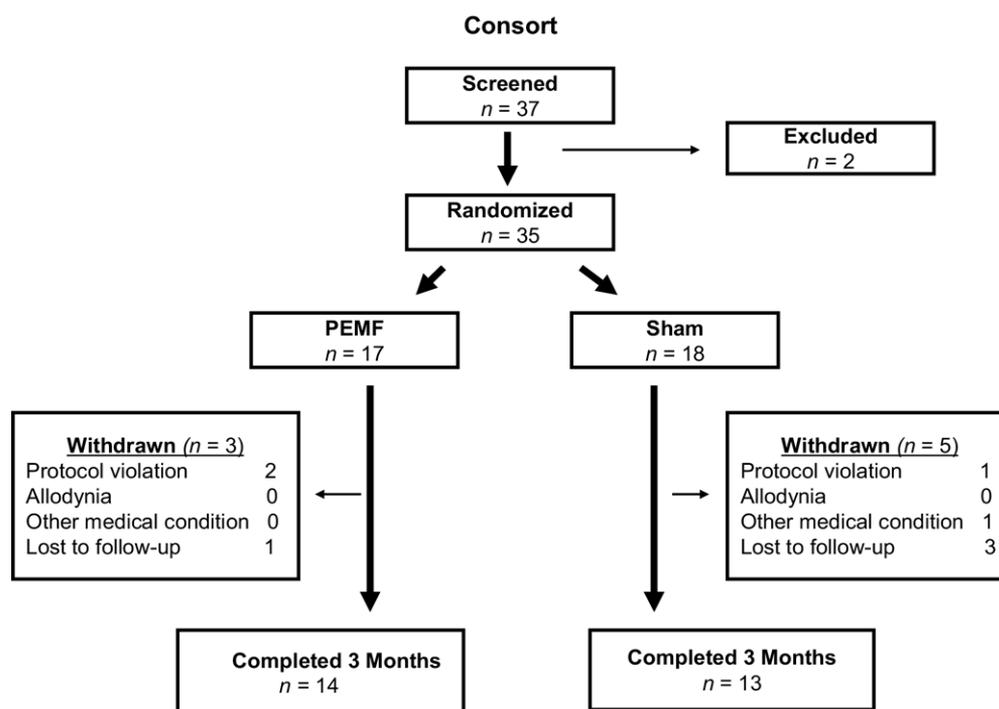
Consort

Fig 3. Biopsy consort.

Table 2: Results of Pain and Sleep Scales

Measures	PEMF (n=90)		Sham (n=104)	
	Baseline	Month 3	Baseline	Month 3
PGIC (% much or very much improved)		43.7		30.6*
VAS	5.59±2.26	4.05±2.71	5.45±2.09	4.13±2.47
Sleep	4.63±3.14	3.27±3.08	4.23±3.14	2.96±2.85
NPS 10	60.35±17.83	45.20±21.18	56.53±18.25	44.21±20.85

NOTE. Values are mean ± SD unless otherwise noted.
*$P<.05$.

($r=.57$; $P<.001$). At 3 months, there were significant correlations between NPS 10 and VAS ($r=.77$; $P<.001$). NPS 10 and PGIC ($r=.50$; $P<.001$), and VAS and PGIC ($r=.53$; $P<.001$).

Biopsy Study

There were no statistically significant group differences in baseline ENFD measures. At the distal leg site, there was a nonsignificant trend for an increase in mean ± SD ENFD (crossings) from baseline (1.33±2.04) to 3 months (1.56±2.34) for the PEMF group, while there was a decrease in ENFD crossings from baseline (1.05±1.64) to 3 months (0.83±1.54) for the sham group ($P=.10$). Similarly, there was a nonsignificant trend for an increase in ENFD total from baseline (1.83±2.93) to 3 months (2.21±3.43) for the PEMF group, while there was a decrease in ENFD total from baseline (1.28±2.10) to 3 months (1.03±1.99) for the sham group ($P=.08$). At the distal leg site, 4 (28.6%) of the magnet group and none of the sham group had greater than 0.5 SD increase in ENFD crossings (χ^2 P value=.04; Fisher exact test=.07) (fig 4). No significant group differences were noted between baseline and 3-month values for ENFD (crossings) and ENFD (total) at the distal and proximal thigh biopsy sites. At the distal thigh, Pearson correlation coefficients for all 27 cases revealed moderate associations between 3-month PGIC scores and changes in ENFD crossings ($r=-.40$; $P=.04$) and changes in ENFD total ($r=-.41$; $P=.04$); higher nerve density was related to global improvement. Over the 3 months, an increase in distal thigh ENFD crossings was moderately associated with a decrease in NPS 10 scores ($r=-.49$; $P=.010$); an increase in distal thigh ENFD total was significantly associated with a decrease in NPS 10 scores ($r=-.53$, $P=.006$) (fig 5). There were no significant correlations between changes in distal leg or proximal thigh ENFD and VAS scores.

Blinding

At the end of the study, the perception of patients and physicians, regarding device activity was erroneous in 20% of the PEMF group and 26% of the sham group. In the absence of objective changes in neurologic examination and conduction studies, physician investigators tended to agree with the responses of their patients.

Safety

There were no safety issues or complications except that 4 cases experienced allodynia leading to dropout (sham=PEMF).

DISCUSSION

To our knowledge, this is the first multicentered, randomized, double-blind, placebo-controlled trial of cumulative exposure of PEMF targeting painful feet in subjects with NP from DPN. The results indicate that the key outcomes related to change in pain or sleep disruption were not improved by

PEMF. However, there are some provocative data suggesting that neurobiological changes occurred in the epidermal innervation exploratory substudy. First, PEMF appeared to affect
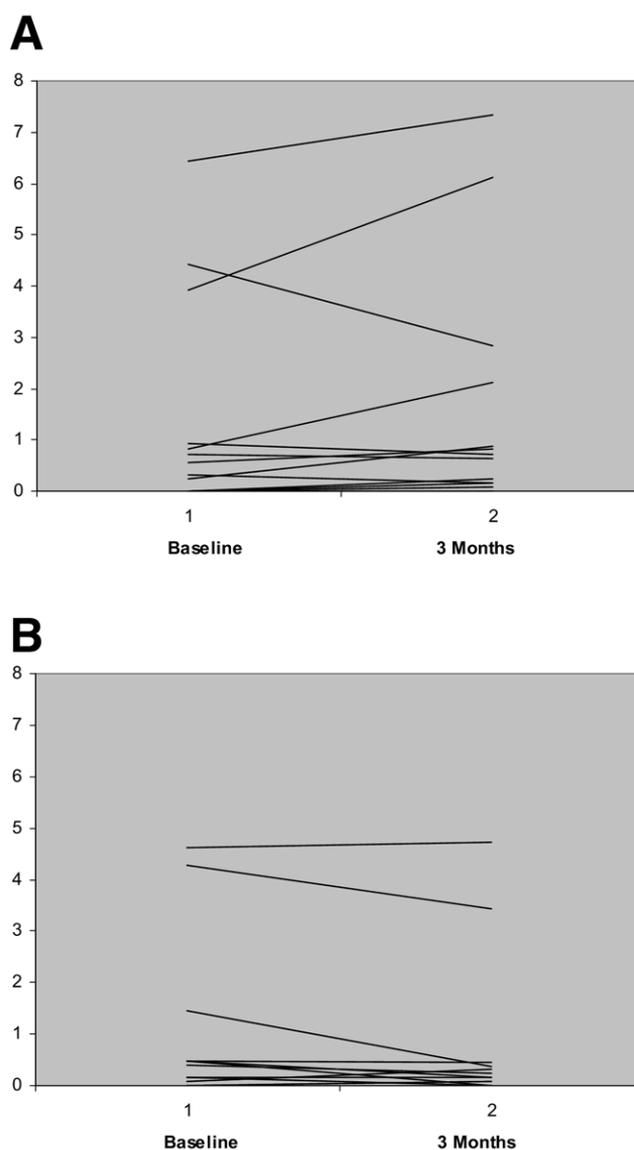
Fig 4. Number of ENFD distal leg crossings in (A) PEMF and (B) sham groups. Dark lines indicate increase in density from baseline to 3 months; light lines indicate decrease or no change.

DPN symptoms, despite the enrollment of patients with relatively advanced DPN (Dyck stage II or III), of whom many subjects were markedly deafferented, particularly at the distal leg site (table 3). Mean ± SD ENFD total for the PEMF cohort at baseline was 1.83±2.93 (normative, 16.6±5.3).[47] This suggests that cutaneous deafferentation does not preclude a beneficial effect of PEMF on NP. Second, we observed no deleterious effect of 12 weeks of PEMF on ENFD, indicating that any effects of PEMF on DPN symptoms are not mediated via injury to nociceptive afferents. Third, we found that 29% of those receiving active PEMF showed at least a 0.5 SD increase in ENFD between the pretreatment and posttreatment time points at the distal leg skin site, while none of the sham group demonstrated such an increase. The exact significance of these changes in ENFD is uncertain and should be cautiously interpreted because of the small cohort size, but it suggests the possibility of a regenerative effect. It was unfortunate that almost one third of subjects failed to return for second biopsy. The significance of reduced itchy pain scores is also unclear but was felt to represent a C-fiber function.

There are several strengths of this study. These include a large homogeneous cohort with stage II and stage III DPN. Additional strengths include the use of 3 validated pain scoring methods representing a composite of the pain experience. The high rate of study completion supports device tolerability. The inclusion of a biologic endpoint (ENFD) in a subset as another measure of neurologic safety is a strength.

Study Limitations

It is difficult to blind subjects reliably given the ease of detecting the presence of magnetism. We believe the placebo effect was as fully controlled as possible using an inert, non-active demagnetized sham device rather than a weak magnet because biological responses have been reported. At completion of the study, the PEMF subjects (48%) reported not knowing whether they had an active or sham device; 32% believed they had an active while 20% believed they had a sham device. For the sham subjects, 56% reported not knowing

Table 3: Epidermal Nerve Fiber Density at Baseline and 3 Months

Measure	PEMF		Sham	
	Baseline	Month 3	Baseline	Month 3
Distal leg				
Crossings	1.33±2.04	1.56±2.34	1.05±1.64	0.83±1.54
Total	1.83±2.94	2.21±3.43	1.28±2.10	1.03±1.99
Distal thigh				
Crossings	5.00±1.68	4.76±2.21	4.49±1.40	4.44±2.30
Total	6.51±2.44	6.26±2.91	5.95±2.08	6.27±3.14
Proximal thigh				
Crossings	7.32±3.11	7.18±2.06	6.58±1.83	7.03±2.41
Total	9.12±3.81	10.28±3.06	8.69±2.83	9.43±3.19

NOTE. Values are mean ± SD.

whether they had an active or sham device; 26% believed they had an active device while 18% believed they had a sham device. Another limitation is that the pain reduction was reflected only in PGIC pain scales and was not significantly different in 3 of the 4 other outcome measures. This could suggest that PEMF may be influencing other aspects of neuropathic dysfunction such as paresthesiae, dysesthesiae, itching, burning, and so forth. Andre-Obadia et al[2,48] believe that pain scores after stimulation are variable and inconsistent, with their reliability increasing in the subsequent 3 to 4 days. Thus the PGIC data reflecting a cumulative response may be more meaningful than VAS and NPS.[49,50] Last, the specific structures potentially influenced in the microenvironment and specific tissue dosimetry at target areas also remain unknown.

CONCLUSIONS

This randomized controlled trial failed to demonstrate a positive effect on pain modulation at this current dosimetry and duration of exposure. However, the potential neurobiologic effects noted from PGIC and skin biopsy data (ENFD) suggest that future studies using a higher dosimetry (3000–5000 G) with a longer duration of exposure and a larger biopsy cohort is warranted to determine whether NP can be modulated by PEMF[51] and influence nerve regeneration.

APPENDIX 1: INVESTIGATORS

The site investigators are listed alphabetically with the principal investigator listed first.

- Misha M. Backonja, MD, Department of Neurology, University of Wisconsin, Madison, WI, Theresa Guiliani, RN (study coordinator)
- Frank DiPalma, DPM, Five County Foot Care, Athens, GA, Stephanie Miller (study coordinator)
- John England, MD, Billings Clinic, Billings, MT, Howard Knapp, MD, Diane Gouine, RN (study coordinator)
- Anthony Geraci, MD, Lutheran Medical Center, Queens, NY, Samara Khorchid, RN (study coordinator)
- Ghazala Hayat, MD, Department of Neurology, St. Louis University, St. Louis, MO, Susan Eller, MA, RN (study coordinator)
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- Eve Holzemer, N.P. Administrative Director
- Jeffrey Jensen, DPM, Diabetic Foot and Wound Center, Denver, CO, Patricia Nelson, RN (study coordinator)
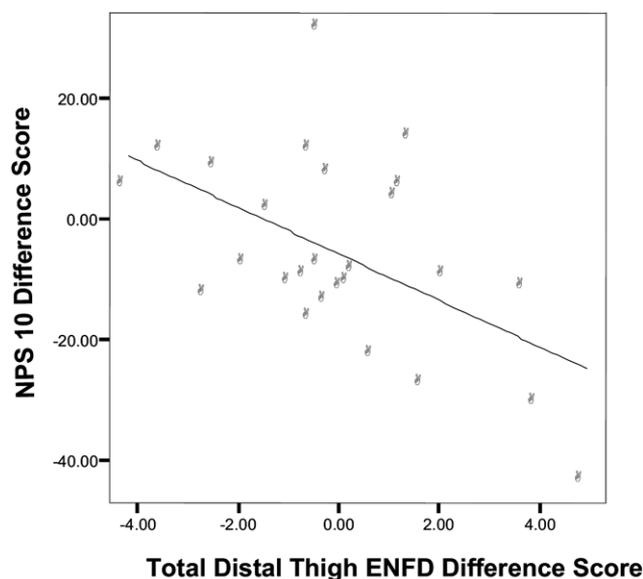
Fig 5. Scatterplot of total distal thigh ENFD: increase in ENFD was significantly associated with a decrease in NPS 10 (difference) scores ($r=-.53$; $P=.006$).

- Sam Kabbani, MD, East Tennessee Neurology Clinic, Knoxville, TN, Tara Jenkins, RN (study coordinator)
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Suppliers

a. Body Energizer; Nu-Magnetics, Inc, Box 572, Port Jefferson, NY 11777-1025.
b. ENF meter, Model UHS; Alpha Lab, Inc, 3005 South 300 West, Salt Lake City, UT 84115.
c. SPSS version 15.0; SPSS, Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.