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

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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 and the Patient’s Global Impression of Change (PGIC). A Visual Analog Scale (VAS), the Neuropathy Pain Scale (NPS), and each participating clinical site approved the study protocol and informed consent analysis, interpretation of data, or article development.

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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.
and reduced VEGF,19,24 impaired voltage-gated channels (sodium, potassium, calcium),13,15,25 protein kinase C dysregulation,19,26 and oxidative stress19,27,28 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 VEGF29-31; reorients Schwann cells32; enhances macrophage activity33 and endoneurial blood flow34; reduces nociceptive afferent signal transduction35-38; reduces free radicals37,39 and oxidative stress33,40; 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 randomization 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

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**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.
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 (b coaxial), 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 meterb (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) 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. NPS composite (NPS 10) scores range from 0 to 100. PGIC 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 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, 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) × 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 × 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) 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
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
groups. Mean 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

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

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

NOTE. Values are mean ± SD unless otherwise noted.

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, narcot-
cics, tricyclics, selective serotonin reuptake inhibitors, or non-
steroidal 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 fol-
low-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=0.04). This result was considered a nonsignif-
icant trend. Group differences from baseline to 3 months were
not significant for VAS (P=0.96), NPS 10 (P=0.58), sleep scores
(P=0.49), 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% reduc-
tion 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=0.048). Subjects who reported higher levels
of itching also reported higher levels of burning at baseline
(r=0.32; P<0.001) and at 3 months (r=0.33; P<0.001).

Correlations Between Pain Measures

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

Fig 3. Biopsy consort.
(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 (χ² 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
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). 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 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 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. 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 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)
- David Herrmann, MD, BCH, Director of Peripheral Neuropathy Clinic and Cutaneous Innervation Laboratory, University of Rochester Medical Center, Rochester, NY, Janet Sawden, RN (study coordinator)
- Eve Holzemer, N.P, Administrative Director
- Jeffrey Jensen, DPM, Diabetic Foot and Wound Center, Denver, CO, Patricia Nelson, RN (study coordinator)
Electromagnetic Fields to Reduce Diabetic Neuropathic Pain, Weintraub

References


