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.

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

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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 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]

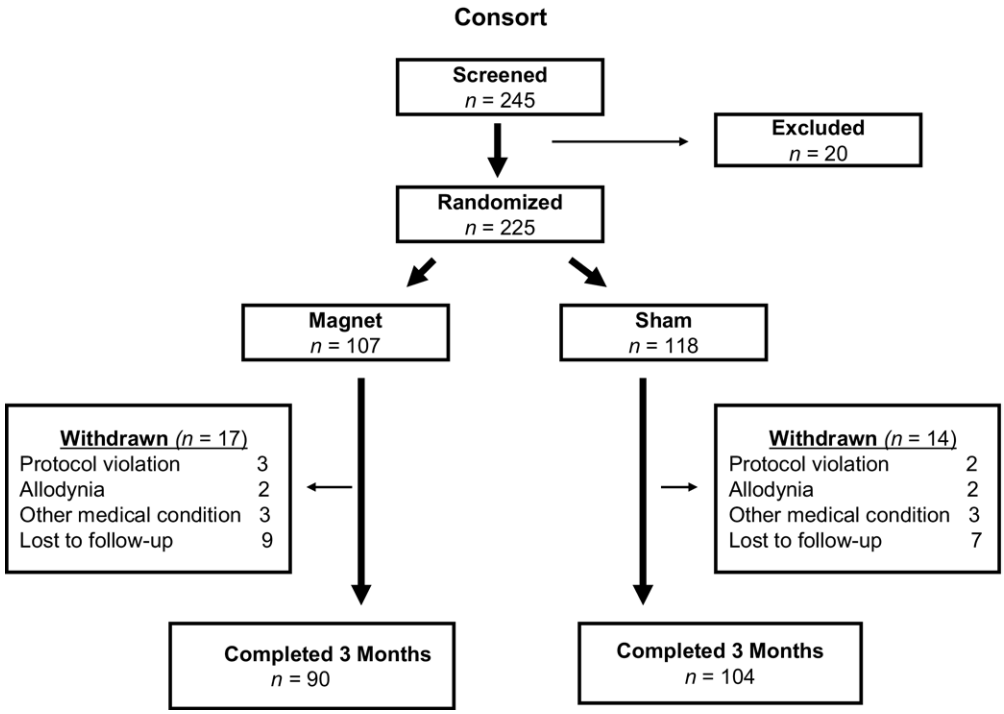

Fig 1. The CONSORT diagram revealing enrollment and outcomes. A total of 245 subjects were screened, and 225 were randomized and enrolled. A 13.8% dropout occurred (31/225) with no safety issues.