Pulsed Magnetic Field Therapy in Refractory Neuropathic Pain Secondary to Peripheral Neuropathy: Electrodiagnostic Parameters—Pilot Study

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Context. *Neuropathic pain (NP) from peripheral neuropathy (PN) arises from ectopic firing of unmyelinated C-fibers with accumulation of sodium and calcium channels. Because pulsed electromagnetic fields (PEMF) safely induce extremely low frequency (ELF) quasirectangular currents that can depolarize, repolarize, and hyperpolarize neurons, it was hypothesized that directing this energy into the sole of one foot could potentially modulate neuropathic pain.* Objective. *To determine if 9 consecutive 1-h treatments in physician's office (excluding weekends) of a pulsed signal therapy can reduce NP scores in refractory feet with PN.* Design/setting/patients. *24 consecutive patients with refractory and symptomatic PN from diabetes, chronic inflammatory demyelinating polyneuropathy (CIDP), pernicious anemia, mercury poisoning, paraneoplastic syndrome, tarsal tunnel, and idiopathic sensory neuropathy were enrolled in this nonplacebo pilot study. The most symptomatic foot received therapy. Primary endpoints were comparison of VAS scores at the end of 9 days and the end of 30 days follow-up compared to baseline pain scores. Additionally, Patients' Global Impression of Change (PGIC) questionnaire was tabulated describing response to treatment. Subgroup analysis of nerve conduction scores, quantified sensory testing (QST), and serial examination changes were also tabulated. Subgroup classification of pain (Serlin) was utilized to determine if there were disproportionate responses.* Intervention. *Noninvasive pulsed signal therapy generates a unidirectional quasirectangular waveform with strength about 20 gauss and a frequency about 30 Hz into the soles of the feet for 9 consecutive 1-h treatments (excluding weekends). The most symptomatic foot of each patient was treated.* Results. *All 24 feet completed 9 days of treatment. 15/24 completed follow-up (62%) with mean pain scores decreasing 21% from baseline to end of treatment (*P = *0.19) but with 49% reduction of pain scores from baseline to end of follow-up (*P < *0.01). Of this group, self-reported PGIC was improved 67% (n = 10) and no change was 33% (n = 5). An intent-to-treat analysis based on all 24 feet demonstrated a 19% reduction in pain scores from baseline to end of treatment (*P = *0.10) and a 37% decrease from baseline to end of follow-up (*P < *0.01). Subgroup analysis revealed 5 patients with mild pain with nonsignificant reduction at end of follow-up. Of the 19 feet with moderate to severe pain, there was a 28% reduction from baseline to end of treatment (*P < *0.05) and a 39% decrease from baseline to end of follow-up (*P < *0.01). Benefit was better in those patients with axonal changes and advanced CPT baseline scores. The clinical examination did not change. There were no adverse events or safety issues.* Conclusions. *These pilot data demonstrate that directing PEMF to refractory feet can provide unexpected short-term analgesic effects in more than 50% of individuals. The role of placebo is not known and was not tested. The precise mechanism is unclear yet suggests that severe and advanced cases are more magnetically sensitive. Future studies are needed with randomized placebo-controlled design and longer treatment periods.*

Key Words: *Neuropathic pain—Pulsed magnetic field therapy—Peripheral neuropathy.*

Symptomatic peripheral neuropathy is often a painful and progressively disabling condition that traditionally is refractory to treatment.[1] Complex mechanisms and etiologies exist that adversely influence both myelinated and unmyelinated fibers leading to symptomatology. From a pathophysiological standpoint, neuropathic pain is believed secondary to ectopic firing of nociceptive afferent unmyelinated C-fiber axons that are undergoing degeneration.[2] Microneurography has demonstrated that ectopic depolarization is caused by dysregulated expression of sodium and calcium channels.[3,4] Pharmacotherapy is the cornerstone

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approach in the management of neuropathic pain yet currently there are no specific treatments that reverse or arrest progressive peripheral neuropathy.[1] Thus, the search for reliable and new therapeutic strategies is appealing. Because substantial evidence exists that pulsed electromagnetic fields (PEMF) safely induce small electrical eddy currents within the body that can depolarize, repolarize, and hyperpolarize neurons, it was hypothesized that this energy directed to the soles of one foot could potentially influence neuropathic pain scores.[5-12]

STUDY DESIGN

Twenty-four consecutive patients with feet symptomatic from peripheral neuropathy due to diabetes, pernicious anemia, chronic inflammatory demyelinating polyneuropathy (CIDP), mercury poisoning, tarsal tunnel, paraneoplastic syndrome, and idiopathic sensory neuropathy were enrolled in this study between July and November 2002 and met the following criteria: a) neuropathic symptoms of numbness, tingling, burning or pain on a daily basis; b) failure to standard therapies, that is, tricyclics, analgesics, antiepileptics, opioids, acupuncture, neurotrophic vitamins, and so on; and c) ability to keep visual analog scores (VAS) of pain for the duration of the study. Adjectives and numbers appeared on the form for the patients to correlate their pain intensity. Patients were excluded who had mechanical implanted devices or who were pregnant. The most symptomatic foot in each patient received therapy and was studied.

PRIMARY OUTCOME MEASURES

Primary outcome measures were VAS (0-10) scores tabulated daily through the treatment period and also with follow-up scores within 15 days. This would be compared to 1 week of baseline pretreatment scores (VAS). Additionally, at the end of the treatment period, patients would respond to a standardized Patient's Global Impression of Change (PGIC)[13] questionnaire with 7 options describing their response to treatment. Subgroup analysis (VAS scores, nerve conduction velocities [NCV] changes, current perception thresholds [CPT] scores), based on severity and response, would be compared. Secondary endpoints were examination changes.

Baseline electrophysiological tests, that is, NCV, attempted to quantify the severity of the neuropathy and depict if this was axonal or demyelinating. Forced-choice quantified sensory testing (QST) measured by neurometer were performed at baseline to determine the degree of dysfunction. This is a portable, constant sine wave stimulator applied through surface electrodes at 3 frequencies (5 Hz, 250 Hz, and 2000 Hz), and a forced-choice method is used to determine the minimum amplitude of detection. The CPTs are measured with units equivalent to 0.01 mAmperes (mA). The scores were generated as CPTs from 0-10.

This is an open, nonplacebo study with protocol approved by the Phelps Hospital Investigational Review Board (IRB). After a complete description of the study, written informed consent was obtained prior to enrollment. No new analgesics were allowed; however, patients could remain on their current regimens.

DEVICE

Pulsed signal therapy (PST), a variant of PEMF, has been previously described.[14-16] The device generates a pure magnetic field output signal that employs direct current with unidirectional biological frequencies below 30 Hz. The wave form is quasirectangular with measured field strengths generally below 2 mT or 20 gauss. The system is controlled through a pulsed unidirectional magnetic DC field with multiple output frequencies implemented via a free-wheeling diode to optimize the induction characteristics. Various frequency/ amplitude combinations are switched over automatically and are transmitted under continuous control during the treatment period. Induction of treatment takes place during the first 10 min followed by a combination of pulsed signals that deliver the therapy over the remaining 50 min. A 1-h duty cycle timecard is inserted, which starts the induction and subsequent treatment process. This is noiseless and nonthermal. The most symptomatic foot is placed comfortably inside a closed circuit coil for 1 h on 9 consecutive days, excluding weekends (Saturday/Sunday). A time card is inserted, which starts the 10-min induction process followed by 50 min of treatment. The quasirectangular waveforms have a frequency below 30 Hz and a strength below 20 gauss (2 mT). Various patented frequency/ amplitude combinations are automatically sequenced.

MASKING

The investigator (MIW) was not blinded. All patients were informed that this was an open-label trial of active magnetic stimulation. There were no placebo controls. Participants came to the office of MIW for the above treatments.

STATISTICAL ANALYSIS

One-way repeated measures analyses of variance (ANOVA) was used to assess changes in pain scores over the course of the study at baseline, end of treatment, and at end of follow-up. Reductions in pain scores from baseline to end of treatment and from baseline to end of follow-up were tested with a priori contrasts. An intent-to-treat ANOVA was conducted in which the last recorded pain score during treatment was substituted for missing follow-up scores for the patients who completed treatment but did not complete follow-up. For all tests, a p value of 0.05 or less was considered to indicate statistical significance. The Statistical Package of the Social Sciences (Ver. 10.0) was used to analyze the data (SPSS, Inc., 233 South Wacker Drive, Chicago, IL 60606).

FUNDING

There was no funding for this study. Two PST portable devices with duty time cards were provided on loan by Bio Magnetic Therapy Systems, Inc. (Boca Raton, FL). The authors had complete independence regarding study design, data analysis, and manuscript preparation.

DEMOGRAPHIC VARIABLES

All of the 24 feet that were enrolled in the study completed treatment. Of these 24 feet, 15 completed follow-up. Of the 10 female feet and 5 male feet that completed treatment and follow-up, ages ranged from 41 to 85 (M = 67.32, SD = 13.44) and duration of symptoms ranged from 1.33 to 15 years (M = 6.41, SD = 3.78). Etiology of peripheral neuropathy was tabulated to be diabetes mellitus (6), pernicious anemia (2), hypothyroidism (2), tarsal tunnel (3), mercury poisoning (1), prostate cancer (1), hemochromatosis (1), CIDP (2), and idiopathic sensory neuropathy (6).

Nerve conduction studies were performed on 19 patients of which axonal changes (#11) were noted in 58% and demyelinating changes (#8) were noted in 42%. CPT was performed in 11 cases; 5 had advanced scores (9-10), 3 had severe scores (7-8.99), and 3 had mild scores (0-6).

RESULTS

All 24 feet completed 9 days of treatment. However, 9 feet (38%) completed treatment but did not complete follow-up. For the 24 feet enrolled in this study, patient ages ranged from 41 to 85 (M = 67.29 ± 12.43) and duration of symptoms range from 1.33 to 15 years (M = 6.32 ± 3.50).

A repeated measures analysis of variance (baseline, end of treatment, end of follow-up) based on the 15 feet that completed treatment and follow-up demonstrated a statistically significant reduction in pain scores, $F(2,28) = 7.25$, $p < 0.01$, eta-squared = 0.34. Mean pain scores decreased 21% from baseline (6.47 ± 2.64) to end of treatment (5.13 ± 2.59), $p = 0.19$ and decreased 49% from baseline to end of follow-up (3.33 ± 1.78), $p < 0.01$. Self-reported change in overall pain (PGIC) from baseline to end of treatment was collected from patients for the 15 feet. Improvement from baseline was reported for 10 (67%) feet, and no change was reported for 5 (33%) feet.

An intent-to-treat analysis (baseline, end of treatment, end of follow-up) based on all 24 feet demonstrated a statistically significant reduction in pain scores, $F(2,26) = 7.26$, $p < 0.01$, eta-squared = 0.24. Mean pain scores decreased 19% from baseline (6.26 ± 2.44) to end of treatment (5.08 ± 2.57), $p = 0.10$, and decreased 37% from baseline to end of follow-up (3.96 ± 2.27), $p < 0.01$.

Following the above primary analyses, patients were grouped according to their baseline ratings of pain. There were 5 patients (Serlin classification) who reported ratings of 4 or less, which corresponded to mild pain. The remaining 19 patients had baseline scores of 5 to 6 (moderate pain) or 7 to 10 (severe pain). Of the 19 feet with moderate or severe pain that completed treatment, 11 completed treatment but did not complete follow-up. An intent-to-treat analysis (baseline, end of treatment, end of follow-up) based on all 19 feet demonstrated a statistically significant reduction in pain scores, $F(2,18) = 15.83$, $p < 0.01$, eta-squared = 0.47. Mean pain scores decreased 28% from baseline (7.21 ± 1.69) to end of treatment (5.21 ± 2.37),

$p < 0.05$, and decreased 39% from baseline to end of follow-up (4.37 ± 2.29), $p < 0.01$. For the 5 patients with mild pain, there was an 83% increase in mean pain scores from baseline (3.01 ± 03) to end of treatment (5.50 ± 3.32) and a 9% decrease of pain scores at end of follow-up (2.75 ± 1.50). None of the changes for the mild cohort was statistically significant.

SAFETY

There were no adverse events reported.

DISCUSSION

During the past 2 decades, enormous progress has been made in studying the role of magnetic energy on biological systems. Time-varying magnetic fields have been successfully applied to stimulate nerve regeneration in vitro and in vivo.[17-19] Neurite outgrowth has been demonstrated in cell cultures exposed to EMF[8,17-19] and also optical electromagnetic energy.[20] Time-varying weak PEMF of low frequency (3 Hz-3K Hz) had been used in orthopedics and sports medicine, rheumatology, and so on. There appears to be a specific encoding of different tissues to signal amplitude and frequency spectrum. Thus, the rational development of directing time-varying magnetic fields to the sole of the foot is a logical step in attempting to modulate the peripheral ectopic firing afferent C-nociceptors. From an anatomical standpoint, the primary afferent neurons (unmyelinated C-fibers and small A-delta nociceptors) are located in the epidermis and dermis and therefore are easily influenced by cutaneous application of PEMF. Ectopic firing C-fibers with accumulation of sodium channels in area of injury appear to be the principal cause for acroparesthesiae and neuropathic pain.[2-4,21,22] We speculate that the observed antinociceptive effects may be explained by either repolarization or hyperpolarization induced by ELF despite the fact that the specific magnetic flux density at the target area is not known.[23] It is also plausible that the pain reduction in VAS scores is secondary to placebo effect. The results cannot be generalized until a randomized, double-blind placebo-controlled trial is performed. The rationale for PEMF is based on the recognition that injured tissue loses quasirectangular energy and that since time-varying magnetic fields induce small electric currents, it potentially can restore this energy deficit. The waveforms generated are also quasi-rectangular, biphasic, and asymmetric and have a strength of 20 gauss (2mT) or below and a frequency at or about 30 Hz. Irrespective of the precise mechanisms, direct or indirect (electrical or magnetic therapy), interruption and suppression of the afferent signal traffic of the C-fiber's firing pattern is modulated producing an antinociceptive effect. The relative contribution of electrical versus magnetic energy cannot be clarified. Because the intracellular signaling pathway is influenced short term in more than 50% of cases for a 9-day period, the optimum duration and magnitude of energy directed to the soles needs to be considered in a dose/responsive manner.

Despite severe neuropathic pain symptoms, peripheral nerve retains the capacity for recovery of function as long as the nerve cell body remains viable.[28] Although shortcomings of this study include absent placebo controls and biological markers, the fact that more than 50% improvement in a refractory condition occurred is provocative with only 9 treatments. It is noteworthy that when patients were stratified according to severity (VAS, NCV, CPT), those feet that were moderate-severely symptomatic were more magnetically susceptible compared with mild symptomatology. This disproportionate response has been previously noted in several other pharmacological and magnetic studies, suggesting that a moderate amount of neuronal dysfunction must be present to get analgesic benefit.[23,25-27] This observation also provides novel insights about the neuronal circuitry and suggests that a pathophysiological link may exist for differential therapeutic strategies.

In conclusion, the pilot data are provocative for their short-term antinociceptive reduction of neuropathic pain. Precise mechanisms of interaction do not resolve for the role of placebo. Future trials are required with a randomized, double-blind placebo-controlled design utilizing larger cohorts, more prolonged stimulation time, that is, 2-3 months, and so on. This will determine if this modality will be useful in the clinical settings.

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