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A Randomized Controlled Trial of the Effects of a Combination of Static and Dynamic Magnetic Fields on Carpal Tunnel Syndrome

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ABSTRACT

Objective. To determine if a physics-based combination of simultaneous static and time-varying dynamic magnetic field stimulation to the wrist 4 hours/day for 2 months can reduce subjective neuropathic pain and influence objective electrophysiologic parameters of patients with carpal tunnel syndrome (CTS).

Methods. Randomized, double-blinded, placebo-controlled trial of 36 symptomatic hands. Primary endpoints were visual analog scale (VAS) and neuropathic pain scale (NPS) scores at baseline and 2 months and a Patient's Global Impression of Change (PGIC) questionnaire at the end of 2 months. Secondary endpoints were neurologic examination, median nerve distal latencies (compound muscle action potential [CMAP]/sensory nerve action potential [SNAP]), dynamometry, pinch gauge readings, and current perception threshold (CPT) scores. An "active" device was provided *gratis* at the end of the study, with 15 subjects voluntarily remaining within the open protocol an additional 2–10 months and using the preselected primary and secondary parameters.

Results (two months). Of the 31 hands, 25 (13 magnet, 12 sham) had moderate to severe pain (VAS > 4). The VAS and PGIC revealed a nonsignificant pain reduction. NPS analyses (ANOVA) demonstrated a statistically significant reduction of "deep" pain (35% ↓ vs 12% ↑, $P = 0.018$), NPS Total Composite (decreases of 42% vs 24%, $P = 0.042$), NPS Total Descriptor Score (NPS 8; 43% vs 24%), and NPS 4 (42% vs 11%). Motor strength, CMAP/SNAP, and CPT scores were not significantly changed. Of the 15 hands with up to 10 months of active PEMF (pulsed electromagnetic fields) exposure, there was objective improvement in nerve conduction (CMAP = 53%, SNAP = 40%, >1 SD), and subjective improvement on examination (40%), pain scores (50%), and PGIC (70%). No detectable changes in motor strength and CPT.

Conclusions. PEMF exposure in refractory CTS provides statistically significant short- and long-term pain reduction and mild improvement in objective neuronal functions. Neuromodulation appears to influence nociceptive-C and large A-fiber functions, probably through ion/ligand binding.

Key Words. Carpal Tunnel Syndrome; Numbness; Neuralgia; Nerve Conduction; Pain Medicine

Introduction

Entrapment of the median nerve at the wrist is the most common cause of sensory and motor disturbance in the hands and can be progressively disabling [1,2]. Numbness, tingling, and burning within the median innervated hand are the most common symptoms, as well as nocturnal pain and ultimately weakness. Complex mechanisms of compression and ischemia exist that adversely influence the large A-myelinated fibers and small unmyelinated nociceptive C-fibers. From a pathophysiological standpoint, neuropathic pain (NP; numbness, tingling, and burning) is believed secondary to ectopic firing of nociceptive afferent

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unmyelinated C-fiber axons that are undergoing degeneration [3]. Microneurography has confirmed that dysregulated expression of sodium and calcium channels, which accumulate at the site of injury, are responsible for ectopic depolarization [3–6]. It is believed that 3–10% [2,7] of the adult population have carpal tunnel syndrome (CTS). When conventional therapy of splinting and pharmacotherapy fail, surgical decompression has been offered for moderate to severe cases. While usually successful, it is associated with significant complications, limitations, and costs [8–10]. Thus, the search for reliable and new therapeutic strategies is appealing.

Substantial evidence exists that time-varying magnetic fields produce biological effects by safely inducing extremely low-frequency small electrical eddy currents within the tissues that can depolarize, repolarize, and hyperpolarize neurons [11–16].

Prior pilot data using static [17] and pulsed electromagnetic fields (PEMF) [18,19] directed to the carpal tunnel region significantly reduced NP. Since a new, novel device became commercially available that produced a combination of static and dynamic magnetic fields simultaneously, it was hypothesized that this physics-based energy could be directed into the wrists and, potentially, not only influence NP scores, but also modulate median nerve distal latencies (neurotransmission).

Methods/Study Design

CTS is a clinical diagnosis with primary emphasis on sensory complaints (positive and negative or both) and is an important outcome in clinical trials.

Criteria for enrollment were based on the American Academy of Neurology Summary Statement with:

A Neuropathic symptoms of numbness, tingling, or burning pain or weakness in the territory of the median nerve on a daily basis. Symptoms provoked by hand position or sleep. Neurologic examination demonstrating positive sensory/motor changes in the median nerve distribution or presence of Tinel, Phalen, or reverse Phalen signs were required compatible with clinical diagnosis of CTS.

B Failure to respond to standard therapies of splinting, vitamins, steroid wrist injections, pharmacotherapy, analgesics, etc. Symptoms for at least 6 months' duration (chronic).

C No history of other diseases producing similar symptoms (peripheral neuropathy, cervical radiculitis).

D Ability to keep visual analog scale (VAS) scores of NP for the duration of the study.

A randomized, double-blinded, placebo-controlled trial protocol was designed for 2 months with a computer-generated 1:1 random allocation to determine whether 4-hours-daily cumulative therapy to wrists could be an effective treatment for unequivocal CTS with symptomatic NP. From June 2004 through July 2005, we recruited 36 patients with refractory symptoms of CTS who were 18 years of age or older from the private practice of M.I.W. Inclusion criteria revealed that all enrolled patients had an abnormal neurologic examination compatible with the diagnosis of CTS. We utilized electrophysiologic criteria of Dawson [17,20] (motor compound muscle action potential [CMAP] distal latency (DL) > 4.0 milliseconds and sensory DL sensory nerve action potential [SNAP] > 3.7 milliseconds) as a correlative to the clinical diagnosis of CTS. We did not label or stratify patients according to severity of CTS based on electrodiagnostic data. We included patients with baseline NP scores >4 (VAS 0–10), that is moderate to severe pain, so as to not anticipate any "spontaneous" resolution of symptoms, and because moderate to severe pain subjects tend to be more magnetically susceptible and responsive [17,21,22]. Postoperative patients, pregnant women, or patients with implantable pacemakers were excluded. We also excluded patients with peripheral neuropathy or cervical radiculopathy that might mimic symptoms. Participants were allowed to remain on their current regimens but could not add any analgesics or treatments. They could continue their current activities of daily living. Participants who successfully completed the 2-month trial were provided *gratis* a known "active" device.

Because of unexpected and unanticipated enrollment shortfall and dropouts, all subjects were encouraged to voluntarily continue to keep daily VAS pain scores with this new "active device" for an additional 2–10 months of the study with the same preselected primary and secondary outcomes [23–25]. A practical algorithm was developed that could look at not only short-term effects of exposure to PEMF but now were able to generate long-term data of efficacy and safety (*consort* diagram).

Efficacy Evaluations

Baseline primary measures of pain and sleep interference were gathered for 1 week prior to treatment as well as baseline neuropathy pain scale (NPS) [26,27]. Prespecified secondary outcome measures were also used for comparison.

Primary Outcome Measures

A. The VAS [28] is a self-report estimate of pain symptoms measured on an 11-point Likert scale (0 = absent, 10 = worst pain). Participants were asked to rate their pain three times daily and at the same time to represent mean daily pain. This scale is widely used to evaluate pain and has validity and reproducibility [23–25].

B A sleep interference score (VAS 0–10) [22] was tabulated once daily to determine the effects of NP on quality-of-life sleep.

C The Neuropathy pain scale (NPS) [26,27] assessed 10 pain descriptors at baseline and at the end of 2 months. There was NPS Composite Score (NPS 10), NPS Total Descriptor Scores (NPS 8), NPS nonallodynic score (NPS NA), and NPS 4 score (standardized sum of items sharp, hot, dull, and deep pains). The NPS scale ranged from 0 to 100, and the NPS 8, NPS NA, and NPS 4 scales were transformed to range from 0 to 100. Hands included in the assessment had moderate to severe baseline pain, which was defined as having at least four NPS items with scores of 4 or higher.

D Patient's Clinical Global Impression of Change (PGIC): subjects select one of seven options describing response to treatment, ranging from "very much improved" to "very much worse."

Secondary Outcome Parameters

A Neurologic examination of sensation over the median nerve as well as to presence of Tinel, Phalen, or reverse Phalen signs. Examination of hand strength Utilizing Medical Research Council Guidelines 5/5 [29], and presence of thenar atrophy.

B Grip strength was measured with a hydraulic hand dynamometer (Baseline by Fabrication Enterprise, Elmsford, New York) with the patient seated and elbow fully extended. Handle was set at the second position. After an introductory grip trial, each subject performed the grip test, "press, hold and release," three times after appropriate resetting with a 15-second interval. The mean score was calibrated in pounds [30,31].

C Pinch strength was measured with a calibrated hydraulic pinch gauge (Baseline by Fabrication Enterprise) measuring the pressure between the thumb and index finger with the patient seated, elbow flexed, and wrist in neutral position. After an introductory trial of "press, hold and release," three repeat trial measurements were taken with appropriate resetting at 15-second intervals. The mean score was calibrated in pounds [32,33].

D Electrophysiologic studies: median nerve distal motor and sensory latencies were performed using standardized surface electrode techniques. These were performed by M.I.W., who was blinded during the first 2 months. Standard filter settings for motor (2–10,000 Hz) and sensory (10–5,000 Hz) were used with supramaximal stimulation and skin temperature >32°C. Latencies were measured from the stimulus onset to the initial negative response, and amplitudes were measured from baseline to negative peak. The SNAP was recorded orthodromically with ring electrodes on digit 4 around the proximal (active) and distal reference interphalangeal joint [34–36]. The ground electrode was attached to the distal wrist. The motor latency (CMAP) was defined as the time from the antidromic stimulus to onset of the nerve signal of abductor pollicis brevis. All studies were performed using TECA TD10 (TECA Corporation, Pleasantville, New York) with standard lengths. Electrophysiologic criteria used to define abnormality were SNAP DL >3.7 milliseconds and CMAP DL >4.0 milliseconds [20]. Subjects with conduction block were included. Specific median-ulnar nerve conduction differences ipsilaterally were performed so as to have an unequivocal cohort of CTS from an electrodiagnostic standpoint.

E Current perception threshold (CPT; Neurometer, Neurotron, Inc., Baltimore, MD): a psychophysical instrument utilizing AC current at 5-, 250-, and 2,000-Hz frequencies to index finger was used to assess a small subpopulation of nerve cells by forced-choice computer-generated algorithm. The 2,000-Hz stimulus evokes response from large myelinated A-beta fibers, 250 Hz evokes responses from A-delta fibers, and 5 Hz evokes responses from small unmyelinated C-fibers [37,38].

Fifteen hands (patients) voluntarily agreed to remain in the above protocol for an additional 2–10 months. Primary and secondary outcome

Figure 1 Device attached to wrist by Velcro worn 4 hours per day.

measures continued to be tabulated. The results provided intermediate- and long-term data related to daily exposure to the PEMF device.

Device

Description (Fig. 1)

This patented device (Biaxial Super Mini [Mx^2R] by Nu-Magnetics, Inc., Spokane, WA) measures 2″ in diameter and 1″ in height, and is worn with a Velcro strap similar to a wristwatch. It is noiseless and nonthermal. Its main component is a spherical permanent magnet, 1150G, 3/8″ in diameter, that rotates in two perpendicular directions simultaneously producing biaxial magnetic rotation (Mx^2R) and oscillating polarities up to 1,200 r.p.m.—20 times per second. It is driven by a 2-V DC micromotor, which is shielded 1 inch away and produces a negligible back electromotive force (EMF). The device is powered by three 1/4 AAA rechargeable Nickel Metal Hydride batteries. The devices were calibrated once at the factory and coded in conjunction with a statistician.

Field Measurements

Static (DC) magnetic fields were measured with a Lakeshore model 450 gaussmeter equipped with a unidirectional Hall effect probe having a diameter of 1.5 mm. Time-varying magnetic fields were measured with a 65-turn 5-mm diameter search coil calibrated to measure the induced electric field in mV/cm for a target diameter of 10 mm [39]. The search coil output was displayed on a Tektronix model 5441 oscilloscope (Beaverton, OR). The results are as follows:

1. The static component (DC) normal to the device, i.e., projected toward the target, averages about 50 gauss across a plane parallel to, and the same size as, the surface of the magnet at 1 mm, and drops to about 3 gauss on an identical plane at 2 cm from the surface of the magnet. However, these amplitudes only appear in a very small volume (several cubic millimeters) of tissue because of the small diameter of the magnet (approximately 1 cm). The mean magnetic field over a surface area of approximately 2 cm^2 at 2 cm from the magnetic surface is approximately 0.5 gauss, which is of the same order as the earth's magnetic field.
2. There is a time-varying magnetic field (AC) due to the rotation of the magnet which generates a sinusoidal waveform at approximately 20 Hz, which induces a peak electric field 1 mm from the magnet surface of about 0.5 mV/cm, dropping to 0.1 mV/cm at 2 cm. The mean peak magnetic field at 20 Hz over a surface area of approximately 2 cm^2 at 2 cm from the magnet surface is approximately 0.5 gauss.

Biophysical Considerations

The electromagnetic field applied to the tissue target consists of a DC and an AC magnetic field, which exist simultaneously. A DC component of several gauss in situ has been well documented to relieve musculoskeletal pain. The AC component does not induce a large enough electric field to be detectable above background thermal noise in an ion-binding target. Therefore, the entire stimulus is magnetic. However, Larmor precession frequency activation may be present.

The dual-axis revolution causes the magnetic sphere to turn in all directions, generating flux lines across magnetically sensitive tissue elements, i.e., ions in nerves and cells and lipid neuronal membranes. Periodically changing angles produces varying intensity of force and direction on the underlying magnetically sensitive elements in the tissue according to the Lorentz force and Faraday's Law [40] and Lenz's Law [41]. There is also induction of electrical charges within the tissue, thereby influencing signal transduction.

Utilization of the wrist devices was demonstrated to each patient and/or family representative when present. Guidelines for 2-hour utilization twice a day were provided, and regular activities of daily living and hobbies were encouraged.

Mechanical breakdowns of devices were anticipated, and the statistician created similar coded rescue devices in case of malfunction so that there

would be continuous treatment without any time lapses.

Investigational Review Board

Phelps Memorial Hospital Investigational Review Board (IRB) reviewed and approved the 2-month protocol. All patients provided written informed consent to participate in this study, as well as being offered a free "known active" wrist device at the end of the 2-month study for their participation with a commercial value of $100. Because the open-label portion constituted analysis of similar outcome data, using patients as their own control, it did not require additional IRB approval. However, informed consent and options were provided to each subject.

Role of the Funding Source

This study was funded by Nikken, Inc. The sponsor had no part in the design of the study, collection of the data, data interpretation, or final manuscript preparation. The authors had full access and independence and were totally responsible for manuscript submission. There was no sharing of data.

Safety

Safety analyses assessing the incidence and severity of adverse events were tabulated throughout the study. The severity of adverse events was pregraded on a three-point severity scale (i.e., mild, moderate, and severe). Withdrawal/dropouts were questioned. We advised patients to keep devices away from credit cards and not to use them near the computer so as to avoid potential damage to magnetically sensitive products and also break the coding. Subjects could otherwise continue normal activities of daily living.

Statistical Analysis

Two (magnet, sham) × two (baseline, end of month 2) repeated measures analyses of variance (ANOVA) were used to assess change in pain scores and secondary outcomes over the course of the study. A statistically significant treatment group × time interaction indicated greater change from baseline to the end of month 2 for one of the treatment groups. Independent sample *t*-tests were used to test for possible baseline differences in mean scores and for the PGIC at 2 months. With a statistically significant baseline difference, analysis of covariance (ANCOVA) was conducted with baseline scores as a covariant, treatment group as the independent variable, and month 2 scores as the dependent variable. Chi-square tests were used to assess change in nerve conduction test categories from baseline to month 2.

All tests were two-sided with a level of significance set at $P < 0.05$. The statistical package for the Social Sciences (version 12.0.2) was used to analyze the data (SPSS, Inc., Chicago, IL).

Results

The demographic and clinical characteristics of the two groups at baseline are summarized in Table 1. Twenty-three female and 13 male individuals were enrolled and randomized with similar characteristics of age, duration of symptoms, etc. There were five dropouts (4 female, 1 male). Of the 27 hands with complete NPS data, 21 (11 magnet, 10 sham) had moderate to severe pain (78%) (Fig. 2). Means and standard deviations for Composite NPS measures and VAS scores for hands with *moderate/severe pain* at baseline and 2 months are displayed in Table 2. The mean baseline scores reflect that the active magnetic

Table 1 Demographics of the study sample

	Moderate to Severe Baseline Pain		Mild Baseline Pain	
Characteristic	Magnet ($n = 11$)	Sham ($n = 10$)	Magnet ($n = 1$)	Sham ($n = 5$)
Age (years)				
Mean ± SD	65.82 ± 14.79	59.60 ± 4.18	64.17	59.80 ± 10.80
Range	41–86	37–78		46.74
Gender (N)				
Female	8	5	1	3
Mean ± SD	3	5	0	2
Years since CTS onset				
Mean ± SD	3.96 ± 3.29	4.18 ± 4.52	7.00	1.38 ± 0.84

CTS = carpal tunnel syndrome.

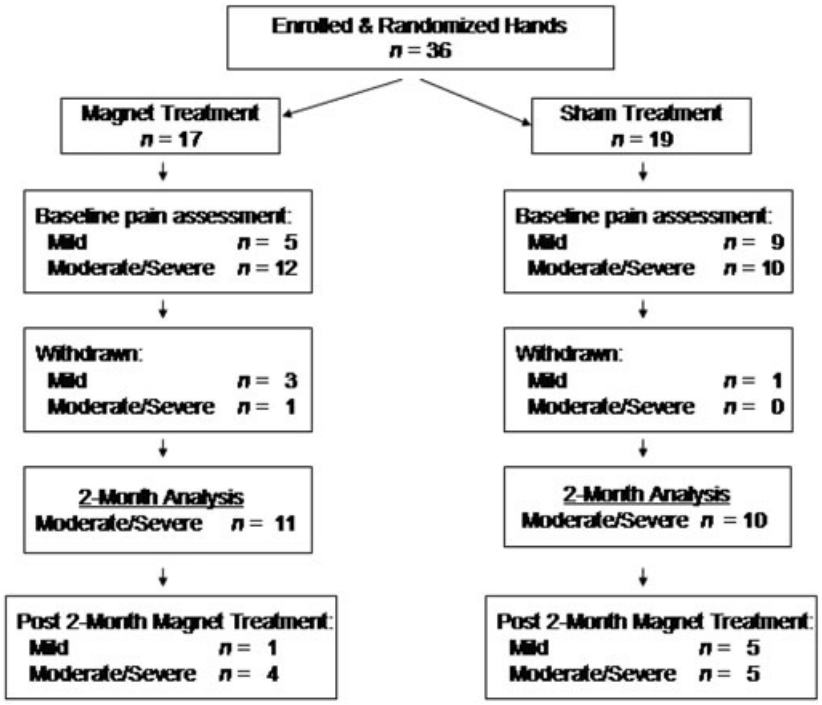

Figure 2 Case flow diagram.

groups tended to have more intense symptomatology. Effect sizes (η^2) for the statistically significant results ranged from 0.20 to 0.26. According to Cohen [23], values in this range indicate large effect sizes.

NPS Total Composite

There was a statistically significant reduction ($P = 0.04$, $\eta^2 = 0.20$) in mean pain scores for magnet treatment hands when compared with sham treatment hands (42% for the magnet group vs 24% for the sham group).

NPS 8 Total Descriptor Score

There was a statistically significant reduction in mean pain scores for magnet treatment hands when compared with sham treatment hands (43% vs 24%, $P = 0.04$, $\eta^2 = 0.20$).

NPS 4

NPS 4 is an average of "sharp," "hot," "dull," and "deep" pain scores. Although there was a significant difference ($P = 0.02$) from baseline to month 2 for magnet hands (42%) when compared with sham hands (11%), when the baseline group difference was statistically controlled, the month 2 difference was not significant ($P = 0.17$).

NPS "Deep" Pain Score

There was a significant reduction ($P = 0.02$, $\eta^2 = 0.26$) in mean pain scores from baseline (M = 7.45, SD = 2.66) to month 2 (M = 4.82,

Table 2 Primary outcome data moderate to severe hand pain

	Magnet (N = 11)		Sham (N = 10)	
Measures	Baseline M (SD)	Month 2 M (SD)	Baseline M (SD)	Month 2 M (SD)
VAS	6.82 (2.08)	4.15 (2.13)	5.17 (1.54)	3.78 (2.27)
NPS 10	63.00 (15.90)	36.27 (19.61)	49.60 (14.39)	37.60 (15.36)*
NPS 8	58.18 (17.54)	32.95 (19.04)	45.38 (14.77)	34.50 (15.69)*
NPS NA	63.52 (16.47)	36.25 (20.48)	50.88 (15.37)	38.75 (14.31)
NPS 4	68.18 (21.22)	39.77 (23.76)	49.00 (16.17)	43.75 (18.15)†
Sleep	5.06 (2.91)	3.29 (2.48)	3.45 (3.11)	1.10 (1.37)

* $P < 0.05$.
† ANOVA $P < 0.05$; ANCOVA $P = 0.17$.
NPS = neuropathic pain scale; VAS = visual analog scale.

SD = 3.13) for magnet hands (35% decrease) when compared with the change from baseline (M = 5.10, SD = 3.51) to month 2 (M = 5.70, SD = 2.34) for sham hands (12% increase).

VAS

The reduction of mean VAS scores for magnet hands (39%) was not statistically different from sham hands (27%).

Secondary Outcomes

There were no group differences in reduction of sleep scores. PGIC scores at month 2 were not different between groups ($P = 0.12$; power < 0.30, Fisher's exact test = 0.19). Motor strength, distal latencies (CMAP/SNAP), and CPT scores were unchanged.

Nerve Conduction (2 Months)

There was no significant difference in the 13 active vs 18 sham, except in the latter group there were six cases of clearcut electrophysiologic deterioration.

Follow-up Past the 2-Month Study

Pain

There were too few magnet hands with complete follow-up data to conduct statistical analyses. However, it is noteworthy that for five sham hands which had moderate to severe baseline NP and had data for magnetic treatment for 4 months, there was a significant ($P = 0.03$) decrease (47%) in NPS NA scores from 2 months (M = 45.50, SD = 17.27) to 4 months (M = 24.00, SD = 18.51). For these five hands, there was a nonsignificant 14% decrease in NPS NA scores during baseline to 2-month sham treatment. There was also a significant ($P = 0.02$) decrease (42%) in NPS pain "intensity" scores from 2 months (M = 4.80, SD = 2.17) to 4 months (M = 2.80, SD = 2.39). For these five hands, there was a nonsignificant 25% decrease in NPS pain intensity scores during baseline to 2-month sham treatment.

Nerve Conduction

Of the 15 hands with at least 2 months and up to 10 months of PEMF exposure (mild, moderate, severe), improvement in nerve conduction (CMAP 53%, SNAP 40%, >1 SD) was noted. There were no serial changes in the two subjects with conduction block (absent SNAP/CMAP) and six additional hands with only absent SNAP (Table 3). Serial change with improvement was noted on clinical examination (40%), subjective pain scores (50%), and subjective PGIC (70%). For a number of outcome measures, mean scores for the magnet group are higher at baseline than for the sham group, and they decrease more than the sham group. Although it is unlikely that regression toward the mean would explain all of these changes, it is plausible that, on average, scores that are more extreme may decrease without regard to treatment regimen. (Table 3 does not include group membership because *all* cases displayed have at least 2 months of magnetic exposure.)

Table 3 Baseline and final changes in nerve conduction values for hands with magnetic treatment after 2 months

CMAP		SNAP	
Baseline	Final	Baseline	Final
3.8	4.6	3.8	3.4
7.4	7.4	10.8	7.4
4.1	3.7	Absent	Absent
5.1	Absent	Absent	Absent
4.2	3.8	5.2	4.5
3.8	3.8	4.2	4.5
5.1	4.3	4.3	3.4
8.3	5.0	8.2	5.0
4.0	4.6	3.8	4.0
3.3	2.8	3.4	2.5
5.5	6.1	4.8	Absent
6.4	6.4	Absent	Absent
Absent	6.1	Absent	Absent
7.0	6.2	7.2	Absent
8.4	7.3	Absent	Absent

CMAP = compound muscle action potential; SNAP = sensory nerve action potential.

Of the 17 hands randomized to magnet treatment, four dropped out; of the 19 hands randomized to sham treatment, one dropped out. The sham device subject felt worse and requested surgery. Three of the five did not utilize the device because they changed their minds or were too busy to maintain the protocol or spontaneously felt better. Four devices (1 active, 3 sham) had mechanical problems and could not hold the 2-hour battery charge. The statistician maintained backup (rescue) similar marked devices. These were given on four specific occasions. Patients found the device easy to wear, similar to a wristwatch (Fig. 1). There were no adverse events noted throughout the study.

Discussion

To our knowledge, this is the first published, randomized, placebo-controlled trial using physics-based time-varying, biaxial PEMF directed to the carpal tunnel with secondary open-label extension

to investigate intermediate- and long-term biological effects as regards efficacy and exposure. Statistically significant pain reduction was noted in the moderate to severe cohort in all three primary outcome pain measurements (VAS, NPS, PGIC). Despite the fact that we could not meet initial recruitment and retention goals, it is possible that the small cohort's results may be generalizable to a larger cohort. The electromagnetic field applied to the target consists of a DC and an AC magnetic field, which exist simultaneously. Although the specific target dosimetry is unknown, we speculate that 5–23 gauss was constantly present in the carpal tunnel region. There is little doubt that PEMF produces substantial biological effects on bone and soft tissues [41–43]; yet, the precise mechanisms are undetermined. It has been presumed that voltage-dependent ion/ligand binding and ion transport at the cell membrane is the most likely target area [44,45]. There are three models which have been proposed to provide a mechanism for the bioeffects of weak AC/DC magnetic field combinations. The ion cyclotron resonance and ion parametric resonance models [46–48] attempt to explain how ion movement near a binding site or through a membrane channel can be enhanced with specific combinations of AC and DC magnetic fields and do not predict enhanced effects with static fields only. The third model, the Larmor precession model (LPM), predicts effects starting at approximately 0.1 gauss from either DC or AC/DC magnetic fields [39,40,49]. Larmor precession describes the effects of exogenous magnetic fields on the dynamics of ions in a binding site. A bound ion in a static magnetic field will precess at the Larmor frequency. The LPM proposes that the biochemical reactivity of a bound ion may be affected by changes in its spacial orientation within the binding site. Larmor precession converts the exogenous magnetic field amplitude into a frequency determined by the charge and the mass of the ion. Each Larmor precession frequency determines the minimum time for the bound ion to reach reactive orientation(s) at the binding interface. The LPM predicts a bound ion will accelerate faster to preferred orientations in the binding site with increasing static magnetic field strength. This can increase binding rate with a resultant acceleration in the downstream biochemical cascade. Addition of an AC magnetic field to a bound ion already precessing in a binding site in the presence of a static field will modulate motion with peak effects at multiples of the Larmor frequency. This means that the addition of an AC component to a DC magnetic field could enhance the effect of the DC component despite the weak AC field generated by this device.

Adey and Chopart [50] suggest that membrane surface glycoproteins with a polyanionic structure may function as sensing sites for EMF. It is known that dysregulated expression of sodium, potassium, and calcium channels are responsible for symptoms and hyperexcitability of cells producing paresthesias and NP [51–53]. Neuronal injury can trigger the above with the physiological consequences of altered pattern of impulse generation with repetitive and ectopic firing. We speculate that PEMF induces cellular repolarization at the membrane level [50] with changes in voltage-gated sodium and calcium channels, which accumulate at the site of axonal injury or segmental demyelination. Additional mechanisms that may be relevant are that PEMF could stimulate and recruit inactive C-fibers [22,54] or specifically stimulate A-delta fibers producing inhibition. One of the most frequently suspected transduction pathways for EMF bioeffects is Ca^{2+} binding to calmodulin (CaM) [39,55]. The Ca/CaM interaction regulates many biochemical cascades involved in pain relief and tissue repair, and static magnetic fields have been reported to accelerate this up to twofold [56,57].

Based on studies by Ochoa and others [5,6,51–54,58,59], it appears that the small unmyelinated C-fibers and small myelinated A-delta fibers significantly produce NP. Ectopic firing, specifically of the C-fibers, has been considered to be the cause of acroparesthesias and NP. At a cellular level, we can speculate that remodeling or transcript expression effects on voltage-gated sodium channel and calcium channels occur.

Interactions between nociceptors, neurons, axons, and axoplasmic flow may be *frequency* dependent. It is well known that axons that arise from cell bodies are the cell component most sensitive to electrical and magnetic stimulation producing action potentials. Of particular interest is the fact that preferential stimulation of A-delta fibers occurs at lower frequencies (<5 Hz) [60,61], whereas high-frequency (>100 Hz) stimulates unmyelinated C-fibers and that at higher frequencies, disruption of neuronal circuitry occurs [60,61]. In terms of the predictions of the LPM, a resonance condition at which Ca^{2+} binding will be fastest could occur between 20 and 25 Hz for the mean magnetic field amplitudes applied to the target tissue in this study. The rotating magnet pro-

duced a sinusoidal field at approximately 20 Hz, remarkably close to the conditions required for Larmor resonance. Of course, this resonance condition will not be uniformly produced within the entire inflamed target site because of the small magnet size and the variability of magnet placement and tissue thickness within the patient population. It is interesting to compare the results of this study with those of a previous study wherein a constant 24-hour exposure with static (350 gauss) magnetic field (no AC field) applied to the wrist produced significant pain relief in a similar patient population [17], with exposures for 1 month. The current study with this novel device required only 2 hours of exposures twice a day.

While not overly impressive, there was at least a 10% improvement (1 SD) in distal nerve conduction latencies (CMAP 53%, SNAP 40%). This observation agrees with prior pilot data and static magnetic wrist studies and correlates with the concomitant clinical reduction in NP. Additionally, there is no consistent correlation between DL readings and intensity of pain in the literature. Selective large A-beta fiber neuromodulation is presumed to occur. It is unlikely that regression toward the mean would explain all of these changes [62]. However, we acknowledge that both carpal tunnel symptoms and electrophysiology can change spontaneously. We did not include a nontreated group for 10-month assessment neurophysiologically. Prior studies by Weintraub using nonthermal low-level laser 830 nm [63], electromagnetic energy exposed to the carpal tunnel region, clearly demonstrated both significant serial weekly improvement in neurotransmission (CMAP, SNAP latencies) and reduction in VAS pain scores.

Thus, it is reasonable to assume that neuromodulation of the afferent signaling mechanism is occurring, but uncertainty exists as to the specific mechanisms. Additional possible biologic factors that may be relevant include activation of neurotransmitters and growth factors [64], increased blood flow and influenced free radicals [65], possible stimulation of dorsal root ganglion cells [22,66], and anti-inflammatory response [63,67] directed to the nine tendons around the median nerve, thereby reducing intracarpal pressure. At this stage, it is impossible to determine the precise mechanism of anti-nociceptive effects.

Strengths of this study include: community-based recruitment of typical patients; randomized, placebo-controlled design; use of validated outcomes [68]; and performance of nerve conduction and CPT by one physician and one technician, respectively. This minimized selection bias. The open-labeled extension provided heretofore new information regarding safety and efficacy with long-term follow-up.

Limitations include a small underpowered cohort, use of self-report questionnaires of pain, and the possibility of a placebo response during the open phase of the study. We arbitrarily chose 4 hours per day of treatment as the optimal approach, but perhaps 6 or more hours per day is better and more effective. We also enrolled patients who described their perceived pain as moderate to severe; yet, their VAS pain scores were <4 (0–10). There was also uneven participation in the extended portion with individuals stopping arbitrarily. Despite these inherent limitations, modest pain relief, improvement in sleep, and neurophysiologic improvement was achieved in a refractory condition. Given the lack of a larger study cohort, lack of 10-month, nontreatment cohort neurophysiologically, the results need to be confirmed in a larger, placebo-controlled trial of comparable duration.

In conclusion, there is little doubt that time-varying PEMF produce neuro-biological effects, and our novel data suggest that this unique physics-based device generating AC and DC magnetic fields simultaneously directed to the carpal tunnel is an attractive nonsurgical approach that is safe, and can achieve statistically significant short-, intermediate-, and long-term pain relief and mild changes in neuromodulation. It also has the potential to be utilized as a home treatment. It is conceivable that future longitudinal studies with larger patient cohorts will be able to resolve the uncertainties about the optimal treatment duration and dosimetry that will lead to a neurobiological treatment that minimizes axonal injury, maintains functionality, and delays disability. Lastly, it seems that PEMF appears to work differently from low-level laser therapy. Future studies may also find that a combination of low-level laser therapy plus PEMF will provide superior results [69].

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