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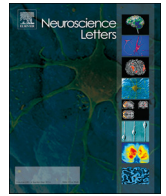
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Research article

Lack of analgesic effects of transcranial pulsed electromagnetic field stimulation in neuropathic pain patients: A randomized double-blind crossover trial

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ABSTRACT

Background: Neuromodulation is nowadays investigated as a promising method for pain relief. Research indicates that a single 30-minute stimulation with transcranial pulsed electromagnetic fields (tPEMF) can induce analgesic effects. However, it is unknown whether tPEMF can induce analgesia in neuropathic pain patients.

Objective: To evaluate the effect of tPEMF on spontaneous pain and heat pain in neuropathic pain patients.

Methods: This study had a randomized double-blind crossover design. Twenty neuropathic pain patients received 30-minutes of tPEMF and 30-minutes sham stimulation. Primary outcomes were pain intensity, pain aversion and heat pain. Secondary outcomes included affect, cognition, and motor function, to investigate safety, tolerability and putative working mechanisms of tPEMF. Outcomes were assessed before, during and after stimulation.

Results: No differences in analgesic effects between tPEMF and sham stimulation were found for pain intensity, pain aversion or heat pain. No differences between tPEMF and sham stimulation were observed for affect, motor, and cognitive outcomes.

Conclusion: A single 30-minute tPEMF stimulation did not induce analgesic effects in neuropathic pain patients, compared to sham. Further study is needed to determine whether prolonged stimulation is necessary for analgesic effects.

1. Introduction

Transcranial pulsed electromagnetic field stimulation (tPEMF) has been reported to show promising results in pain reduction, even after a single 30 min trial [1–4]. If proven effective, this form of neuromodulation may have clinical benefits, e.g. it may be applicable at home. It is currently unknown whether tPEMF would have an analgesic effect in patients with neuropathic pain.

Neuropathic pain is an impairing and often chronic pain disorder caused by a lesion or disease of the somatosensory nervous system [5]. Neuropathic pain-inducing nerve damage can have diverse etiologies,

such as injuries, diabetes, multiple sclerosis, and tumors. Damage to peripheral or central pain pathway neurons causes them to fire inappropriately. This leads to perceived pain and abnormal responses to noxious and innocuous stimuli that are experienced as burning, electrical, throbbing, or stabbing sensations. Traditional treatment of neuropathic pain includes pharmacological, psychological, surgical, and physical approaches [6]. However, these treatments are marked by low effectiveness, and considerable risks and side effects [7–11]. This marks a distinctive need for alternative treatment methods such as tPEMF.

tPEMF consists of specific magnetic waves of a low intensity, in the order of milli- or microteslas, which are applied transcranially in a

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pulsating fashion. The use of several small electromagnets allows for both focally targeted and extended cerebral stimulation. Several animal experiments found analgesic properties of tPEMF [12–14]. This was extended to healthy human volunteers, where researchers, including our own group, also observed a decreased level of subjective pain in response to thermal stimulation after 30 min of tPEMF [1,4].

The first double-blind placebo-controlled randomized trials for pain patients have been published in fibromyalgia. A single 30-minute tPEMF stimulation induced reductions in pain ratings in fibromyalgia and rheumatoid arthritis patients [3]. A setup using a longer treatment period (seven days) seemed to elicit an analgesic effect in chronic fibromyalgia patients with generalized pain (trend effect of $p = .06$), but not in patients with chronic localized musculoskeletal or inflammatory pain [15]. In addition, reductions in self-reported chronic pain scores were found in fibromyalgia patients who received magnetic stimulation once a week for 20 min, for eight weeks [16]. No significant side effects have been reported after prolonged tPEMF.

The mechanism by which tPEMF can induce analgesia is unknown. Besides the possibility of an opioid-mediated effect on pain perception [14], evidence suggests that analgesic effects might occur by influencing the affective component of pain (i.e. the unpleasantness or aversion), rather than sensory aspects or pain intensity. This was suggested after observing tPEMF induced neuromodulation in the insula, anterior cingulate, and hippocampus/caudate [17]. These areas are typically associated with the affective components in pain perception [18]. Further, Martiny et al. [19] found prolonged stimulation with tPEMF (30 min, for 25 days) to have antidepressant effects. Recent findings also emphasize a role of dopamine. Dopamine influences the affective aspects of pain [20], and dopamine regulation is often disturbed in chronic pain patients [21]. Dopaminergic tone has also been found to be sensitive to magnetic stimulation [22,23]. The effect of tPEMF on the affective experience of pain might therefore be an important factor for analgesia.

The current study investigated the analgesic qualities of tPEMF in neuropathic pain patients on both spontaneous pain and heat pain. It was hypothesized that 30 min of tPEMF would reduce perceived pain and increase heat pain tolerance. To explore safety, tolerability and possible mechanisms by which tPEMF might induce analgesia, measures of affect, cognitive performance, and dopaminergic correlates were assessed.

2. Material and methods

2.1. Participants

Twenty neuropathic pain inpatients were recruited at the University Medical Center Groningen (see Supplement 1). Inclusion criteria were age 18–80, being subjectively healthy (with exception of the neuropathic pain), and having a neuropathic pain diagnosis with a “probable” or “definite” Treede Grade (indicating that the presence of the condition has been established by neurological examination) [24]. Exclusion criteria were pregnancy, epilepsy, epilepsy in a first degree relative, use of antiepileptic, prescription or non-prescription psychoactive drugs within the last four weeks (except for pain medication), excessive coffee or alcohol use (> 10 units per day), MRI incompatible implants, manifest signs/symptoms of neurological deficits or a psychiatric disorder, and a history of head trauma with consciousness loss (duration > 5 min).

2.2. Design and procedure

This study had a randomized double-blind crossover design. Participants were tested twice; once they received tPEMF and once sham stimulation. Test moments took place at the same time of the day, with seven days in between. A measurement session was divided into four blocks (see Fig. 1). Participants were familiarized with the testing

regime prior to the first block by practicing all tasks once. Next, questionnaires on affective state were administered and the tPEMF cap was fitted, then the first block started. During the four consecutive fifteen-minute blocks, tasks were administered repeatedly. The first block was the baseline measurement, during which no stimulation was given. During the second and third block participants received either tPEMF or sham stimulation. No stimulation was given during the fourth block.

Within the tPEMF condition, participants received 30 min tPEMF with either high ($n = 10$) or low ($n = 10$) stimulation intensity to monitor for dose-response relationships. Stimulation order and stimulation intensity (high, low) were randomized in a balanced manner. Participants and assessors were blind for stimulation order and intensity. The treatments were administered by running small executable files on a PC of identical size and time stamp, and could not be differentiated. Unblinding took place after completion of both sessions.

2.3. tPEMF

tPEMF was applied with a device designed by our research group. Electromagnetic fields were evoked by nineteen small electromagnets which were attached radially on a regular EEG cap according to the international 10/20 system (see Supplement 2). The magnetic field pattern was based on the “complex neural pulse” which was developed to target pain [25]. High intensity stimulation consisted of a pulse pattern ranging from -2.75 mT to $+2.30$ mT. For low intensity stimulation the pulse intensity ranged from -1.27 mT to $+1.15$ mT. During sham stimulation a zero amplitude magnetic field was delivered. Further details on the device and pulse pattern are described in Kortekaas et al. [4]. Magnetic field strengths were checked with the FH 54 magnetic field strength meter (Magnetic-Physik, Cologne, Germany).

2.4. Primary outcomes

2.4.1. Pain scores

Participants indicated the pain intensity (minute 14 of each block) of the neuropathic pain on a numerical rating scale (NRS) ranging from 0 ‘no pain at all’ to 10 ‘most intense pain imaginable’. Pain aversion was rated on a NRS ranging from 0 ‘not bothering at all’ to 10 ‘worst pain imaginable’.

2.4.2. Warmth detection thresholds (WDT) and heat pain (HP)

WDT and HP were determined twice per fifteen-minute block (minute 1 and 8) using a thermode with a 3×3 cm surface area (Pathway-ATS, Medoc, Ramat Yishai, Israel). The thermode was attached to the patient’s non-dominant normosensitive hand. The thermode heated up from 32 °C at 0.3 °C/s to maximally 50 °C, and cooled down by 3 °C/s. WDT refers to the temperature at which participants verbally indicated that they were certain that the thermode had started to heat up. HP refers to the temperature at which participants described the intensity of heat-induced pain with a 7 on a scale ranging from 0 ‘no pain at all’ to 10 ‘most intense pain imaginable’. WDT and HP were recorded in triple, the median was used for analysis.

2.5. Secondary outcomes

2.5.1. Affective state

The Profile of Mood States (POMS) [26] and the Positive And Negative Affect Schedule (PANAS) [27] were completed before and after each session.

2.5.2. Motor outcomes

The motor variables finger tapping speed and handwriting size were assessed as these are dopaminergic correlates [28,29]. Finger tapping speed was measured twice per block in duplo (minute 4 and 11). Participants pressed a hand counter with the thumb of their dominant hand as often as possible for 20 s. Handwriting size was assessed once per

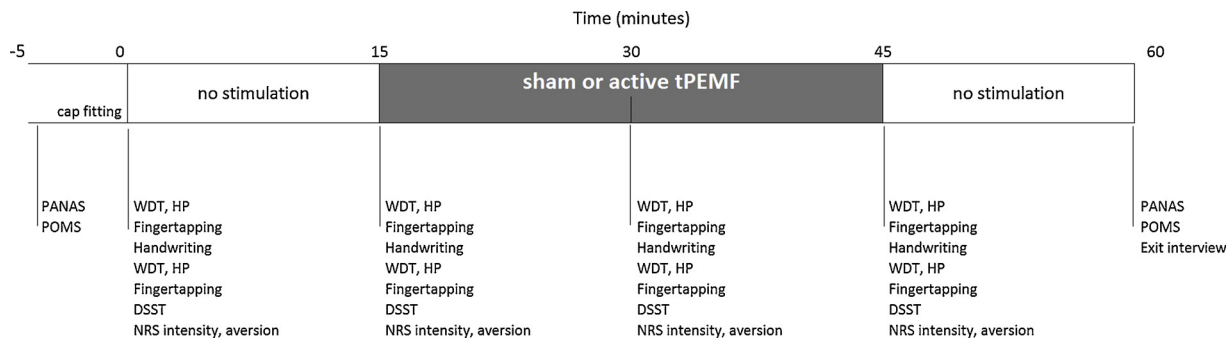


Fig. 1. Overview of the stimulation and measurement protocol.

block (minute 6) by copying a sentence (24 words, 132 characters). The surface of the written text was determined in cm².

2.5.3. Neurocognitive functioning

The Digit-to-Symbol Substitution Test (DSST) [30] was completed once per block (minute 13).

2.5.4. Exit interview

After each session an exit interview took place on side effects and blinding.

2.6. Analysis

Data were analyzed with IBM SPSS Statistics 22. The two stimulation intensity groups were compared at baseline on age (t-test) and gender (chi-square test), significance was accepted at $p = .05$.

First, primary outcomes and affect variables were analyzed with paired-samples t-tests (two-sided) on difference scores between pre and post-measurements to establish whether people benefited from tPEMF. The pre-score was defined as the measurement closest to the start of the stimulation. The first measurement after the stimulation ended was used as the post-measurement. Significance was accepted at $p = .05$.

Second, primary and secondary outcomes were analyzed with three-way repeated measures ANOVAs (RM-ANOVA) on treatment (sham, tPEMF), stimulation intensity (high, low) and time (time of measurement in minutes). Because including the factor stimulation intensity reduces the power, the data were also analyzed with two-way RM-ANOVA on treatment (sham, tPEMF) and time (time of measurement in minutes). The Greenhouse-Geisser correction was applied if the data were non-spherical. Significance was accepted at $p = .05$ for primary outcomes, and for secondary outcomes at $p = .005$ (Bonferroni corrected for 10 tests). The assumption of normality was not met for the difference scores of HP and the subscales of the POMS and PANAS, therefore nonparametric Wilcoxon Signed Ranks tests were performed.

This research was largely exploratory and no literature was available to permit a reliable sample size calculation. Therefore sample size was based on risk estimates and similar types of studies in literature

[1,3,4,15].

2.7. Ethics

The trial was approved by the Medical Ethical Committee of the University Medical Center Groningen. Participants signed informed consent and received no financial compensation. The trial was registered in the Dutch Trial Register (NTR1093).

3. Results

Twenty participants with a mean age of 54.8 ($SD = 14.5$) were included, eleven were male. See supplement 3 for clinical characteristics. Ten participants had definite neuropathic pain, and ten probable according to the Treede Grade. Two patients had an interval of two weeks between measurements instead of one week. None of the patients dropped out. No adverse effects were reported. No relation was found between stimulation order and guess of order (60% was guessed correctly), indicating that blinding was achieved. The low and high intensity stimulation groups differed significantly on gender (low = 90% male, high = 20% male, $p < .01$).

3.1. Stimulation intensity

No significant main or interaction effect of stimulation intensity was found. Therefore, only results of the two-way RM-ANOVA - in which the factor intensity was not included - are presented.

3.2. Primary outcomes

No significant difference was found in change scores of pain intensity ($t(19) = 0.01, p = .91$) or pain aversion between sham and tPEMF ($t(19) = -.053, p = .61$). The RM-ANOVA did show a decreasing trend (Fig. 2) of pain intensity over time ($F(357) = 2.39, p = .08$), however no effect of treatment or an interaction effect for time x treatment ($F(357) = 0.43, p = .73$) was found. A downward trend over time was also found for pain aversion ($F(357) = 2.39, p = .08$), but no

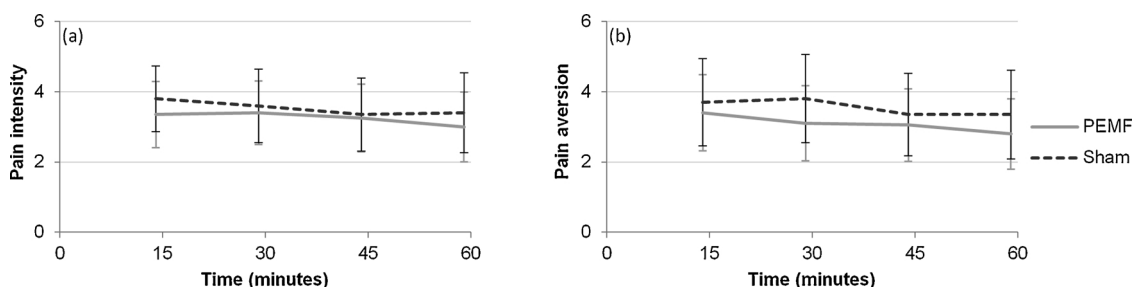


Fig. 2. The average neuropathic pain intensity (a) and aversion (b) during the experiment for sham and tPEMF sessions. Error bars indicate 95% confidence intervals.

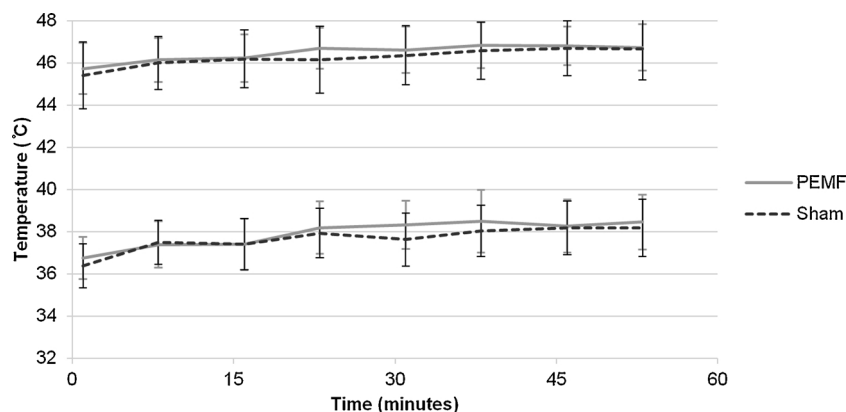


Fig. 3. Course of WDT and HP. The WDT is presented by the lower values, and the HP by the upper values. Error bars indicate 95% confidence intervals.

effect of treatment or an interaction effect for treatment \times time ($F(357) = 0.43$, $p = .73$) was observed. The changes in pain scores per patient can be found in Supplement 4.

Paired-samples t-tests revealed no difference in change scores of the WDT ($t(19) = -0.70$, $p = .50$) or HP ($t(19) = -0.10$, $p = .92$) between sham and tPEMF. RM-ANOVA showed that the HP ($F(756) = 10.12$, $p < .000$) increased significantly during the 60-minute trial, see Fig. 3. No main effect of treatment was found for HP nor an interaction effect for time \times treatment ($F(475) = 0.56$, $p = .69$). Nonparametric testing on HP difference scores confirmed the absence of a treatment effect. WDT increased significantly over time ($F(362) = 11.82$, $p < .000$), but no main effect of treatment was found nor an interaction effect for time \times treatment ($F(7133) = 1.03$, $p = .42$).

3.3. Secondary outcomes

No significant treatment effects were present for positive affect, negative affect or any dimension of the POMS, see Supplement 5. Motor outcomes and the DSST were analyzed with RM-ANOVA; no effect of treatment or the interaction treatment \times time was revealed.

4. Discussion

Our data show that short-duration tPEMF compared to sham does not result in reductions in spontaneous pain or heat pain in neuropathic pain patients. There was a trend reduction of spontaneous neuropathic pain over time during both tPEMF and sham, which indicates the possible presence of a placebo effect. No effect of treatment was observed for warmth thresholds, cognition, affect or motor variables.

Contrary to the expectations based on a study of Shupak et al. [3] in fibromyalgia and rheumatoid arthritis patients, the present neuropathic pain patient group did not benefit from 30-minute tPEMF using an almost identical stimulation wave. Similarly, Thomas et al. [15] could not completely replicate the initial results of Shupak et al. [3] in fibromyalgia patients. In the study by Thomas et al. [15] fibromyalgia patients received 40-minutes tPEMF, twice a day, for seven days. During these days a downward trend was seen in pain severity, indicating that the treatment duration may be an important factor. Possibly our single stimulation of 30 min was not long enough.

Another possible explanation for the lack of effect may be that the presumed therapeutic effect of tPEMF is not applicable for neuropathic pain. Interestingly, Thomas et al. [15] reported positive results for fibromyalgia patients, but no analgesic effects were found when analyzing the complete sample of mixed chronic pain patients. Similar to their group, the present patient sample was heterogeneous. Although all patients were diagnosed with neuropathic pain, etiologies varied considerably among patients. Possibly tPEMF is effective for some pain conditions, but not others. One salient similarity between our patients

was a long duration of illness and a high level of therapy resistance, factors that in itself limit the likelihood of finding a therapeutic effect. It is known that the anatomy and somatosensory system of long-term (neuropathic) pain patients is different from that of healthy people and that this includes changes in cortical thickness [31,32]. Possibly this causes a different or diminished effect of tPEMF in neuropathic pain patients. Another factor of interest is that patients were engaged in cognitive tests while receiving the stimulation, as the effects of neuro-modulation have been found to be different when applied during resting state or performance [33]. Finally, of the participants 85% used medication. It was previously found that anticonvulsants or antidepressants can lower cortical excitability [36,37]. Explorative post-hoc t-tests on change-scores showed no limitative effect of anticonvulsants and/or antidepressants; actually, (non-significant) larger reductions in average pain intensity and aversion in the tPEMF condition were found in patients who used anticonvulsants/antidepressants.

No effect was observed of tPEMF on warmth detection thresholds, indicating that sensory perception was not affected. Patients did seem to experience –expected– desensitization of the skin to innocuous (warmth) and nociceptive (heat) thermal stimuli. Warmth detection and heat pain of the skin showed a strong time dependence, which has also been shown in healthy volunteers [4]. No adverse events or side effects were reported, which underscores the safety of this intervention. The lack of effect on cognitive, motor or affect variables implies that the treatment did not negatively influence neuropsychological functions or the sensory system.

5. Limitations

There were several limitations. First, patients varied strongly in pain; four patients scored zero at pain aversion, indicating that pain was not evidently present. Second, ten patients did not have a definite neuropathic pain diagnosis, but a probable as measured with the Treede Grade. Third, 45% was female. Generally, more pronounced effects of tPEMF have been observed in females [1]. Fourth, this was a small exploratory study, with limited statistical power. Finally, no neurophysiological measurements such as fMRI, EEG or fNIRS were used. There still may have been effects of tPEMF on brain activity level, as changes on brain level have been found to occur prior to behavioral changes [34].

6. Conclusion

With this trial we made a first attempt at treating neuropathic pain patients with tPEMF. In conclusion, a single 30-minute stimulation with the pattern of tPEMF used in this study is not effective in reducing neuropathic or nociceptive pain in severe neuropathic pain patients. The treatment was well tolerated by the patients and gave no adverse

events or side effects. The influence of the duration and number of stimulations may deserve future attention in the investigation of analgesic effects of neuromodulation in chronic pain conditions.

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Competing interests

RK is founder and owner of Magnolia Therapeutics, a company that develops magnetic stimulators and that offers magnetic brain stimulation directly to the public.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.neulet.2019.01.051>.

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