


Pulsed Electromagnetic Field Therapy in the Treatment of Pain and Other Symptoms in Fibromyalgia: A Randomized Controlled Study

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Low-energy pulsed electromagnetic field (PEMF) therapy has been suggested as a promising therapy to increase microcirculation, which is of great concern in patients with fibromyalgia. This study evaluated the effectiveness of PEMF therapy on the treatment of fibromyalgia. A group of 108 women with fibromyalgia were allocated to a 12-week treatment period with an active Bio-Electro-Magnetic-Energy-Regulation (BEMER) device and a similar treatment period with an inactive device. Each patient received active and sham treatments in a random order. Pain and stiffness were assessed on a visual analog scale (VAS, scale 0–100 mm), and functional status was assessed by the Fibromyalgia Impact Questionnaire (FIQ). Mean VAS pain scores before the active and sham treatment periods were 66 (SD 22) and 63 (SD 22), respectively. After treatment periods, mean VAS pain scores had decreased significantly in active treatment, -12 , 95% CI $[-18, -6]$, and in sham treatment, -11 , 95% CI $[-17, -5]$. Similarly, the decrease in stiffness and FIQ index after both treatments was statistically significant. However, per-protocol analysis showed no differences between active and sham treatments at any of the outcomes. This study demonstrated that low-energy PEMF therapy was not efficient in reducing pain and stiffness or in improving functioning in women with fibromyalgia. *Bioelectromagnetics*. 39:405–413, 2018. © 2018 Wiley Periodicals, Inc.

Keywords: pulsed electromagnetic field; magnetotherapy; fibromyalgia; microcirculation; chronic pain; sham treatment

INTRODUCTION

Fibromyalgia is a common syndrome, with a prevalence of approximately 5% in women and 1% in men [Vincent et al., 2013]. It is a condition of soft tissue pain, subjective muscular stiffness, unremitting fatigue, disturbed sleep, and cognitive dysfunction. Numerous possible mechanisms have been postulated to cause fibromyalgia, such as pain hypersensitivity [Gracely et al., 2002], hormonal influences [Sadreddini et al., 2008; Cuatrecasas, 2009], neurotransmitter imbalances [Becker and Schweinhardt, 2012], inflammation [Kadetoff et al., 2012], sleep dysfunction [Moldofsky, 2010; Hussain et al., 2011], mitochondrial dysfunction [Pieczenik and Neustadt, 2007; Gardner and Boles, 2011], small fiber neuropathy [Caro and Winter, 2015], and central sensitivity syndrome [Yunus, 2007; Burgmer et al., 2009; Clauw et al., 2011]. Patients

with fibromyalgia have been reported as having lower peripheral circulation compared to controls, which has been assumed to be due to lower capillary density as well as due to altered autonomic

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regulation [Morf et al., 2005; Choi and Kim, 2015]. Research also suggests that the arteries of patients with fibromyalgia feel stiffer and are less efficient than those of healthy controls [Lee et al., 2011], which may lead to poor circulation and a less efficient blood supply to connective tissues. The exact pathomechanism of fibromyalgia is still unknown, and there is no specific treatment for fibromyalgia.

Electric current therapies have been shown to significantly relieve pain in the short term in fibromyalgia. These include both transcutaneous and percutaneous electrical nerve stimulation [Carbonario et al., 2013; Dailey et al., 2013; Mutlu et al., 2013; Salazar et al., 2017] and a combination of interferential current and ultrasound (US) [Almeida et al., 2003]. Pulsed electromagnetic fields (PEMF), which are one application of magnetotherapy, have also been used for the management of a variety of musculoskeletal conditions [Markov, 2015]. PEMFs differ from other electrotherapy modalities primarily because they are a subthreshold, low-power, and low-frequency electromagnetic waveform [Thomas et al., 2007]. PEMF has shown beneficial effects on osteoarthritis [Li et al., 2013; Bagnato et al., 2016], as well as on peripheral blood circulation [Sun et al., 2016] and healing of skin ulcers [Iran et al., 1990] with a device producing magnetic field intensity of 2.8 mT. However, not all findings on the topic concur [Gupta et al., 2009; Hug and Rösli, 2012]. In patients with fibromyalgia, PEMF with a portable headset device has not shown significant effects on pain [Shupak et al., 2006; Thomas et al., 2007], whereas the application of a whole-body PEMF mat has been suggested to decrease pain in fibromyalgia patients [Sutbeyaz et al., 2009].

A PEMF system called Bio-Electro-Magnetic-Energy Regulation (BEMER, Innomed International, Triesen, Lichtenstein) has been reported as increasing vasomotion and microcirculation for improved organ blood flow using a series of half-wave-shaped sinusoidal intensity variations [Bohn et al., 2013; Klopp et al., 2013]. To date, however, there are no randomized controlled trials (RCT) where the effect of this PEMF device treatment on pain or other symptoms of fibromyalgia has been studied. Therefore, we wanted to test whether low-energy PEMF might have positive responses on symptoms in patients with fibromyalgia possibly via increased microcirculation. The purpose of this study was to investigate whether PEMF therapy can decrease pain and stiffness as well as improve functioning in fibromyalgia.

MATERIALS AND METHODS

Study Design

This study was a randomized, double-blind, placebo-controlled crossover study (NCT02310386; BEMER in the Treatment of Pain in Fibromyalgia). Recruitment and data collection took place between April 2014 and December 2016. The participants were adult women with fibromyalgia. The study protocol was approved by the Ethics Committee of the Central Finland Health Care District, and complies with the Declaration of Helsinki. All participants gave their written informed consent prior to enrollment, and were free to withdraw from the study at any time for any reason without consequences for the care provided.

Participant Recruitment

The participants for this study were recruited through the patient record of the Central Finland Central Hospital. A database search was carried out for patients who had been visiting a specialist between May 2007 and November 2015, and who were diagnosed as having M79.0 (Rheumatism, unspecified), M79.1 (Myalgia), or M79.7 (Fibromyalgia) according to the International Classification of Diseases (ICD). As a result of this search, 1042 patients with established or potential fibromyalgia were sent information about the study and an invitation to participate. A total of 286 subjects indicated their interest in the study, and they were sent a health questionnaire with a prepaid return envelope to assess their preliminary eligibility to participate in the study. In addition to patients' sociodemographic and occupational data, the health questionnaire addressed medical condition, current medication, sleep quality and mood in the last week, alcohol and tobacco use, and treatments received in the previous three months. Eligibility criteria included being a woman aged 18–60 with diagnosed fibromyalgia, persistent moderate or severe pain for more than 12 months, and a pain intensity of 5 or more on a scale of 0–10 within the last seven days. Twenty-three respondents declined to take part in the trial and 263 respondents returned the questionnaire, 133 of which were excluded from the study due to exclusion criteria. The exclusion criteria were as follows: an inflammatory rheumatic disease, another chronic pain disease besides fibromyalgia, mental illness, drug/substance abuse, smoking, intellectual disability, and pregnancy or breastfeeding. The remaining 130 patients were invited to Central Finland Central Hospital for a visit to a physiatrist, who performed a clinical examination to ensure that the participants would not have any limitations to

their study participation and to verify the presence of fibromyalgia. Fibromyalgia was defined according to the American College of Rheumatology's (ACR) classification criteria, and it was confirmed if the patient had widespread pain for at least three months and if she had 11 or more tender points out of 18 specified points [Wolfe et al., 1997]. Fourteen patients did not meet the eligibility criteria during the clinical examinations, and eight participants withdrew from the study, thus leaving a sample of 108 participants for the study. Figure 1 shows the participant recruitment.

Randomization and Blinding

The 108 patients who fulfilled the inclusion criteria were assigned to treatment with real electromagnetic field devices or with sham electromagnetic field devices according to a computer-generated randomization procedure with 30 consecutive balanced blocks of four patients (two active, two sham). Patients, the attending physiatrist (JY), device deliverer (JM), outcome assessor (AH), and statistician (HK) were all blinded to the treatment group assignment.

Treatments

In the first treatment period, 57 patients assigned to active treatment and 51 patients assigned to sham

treatment were instructed to use the electromagnetic field device (BEMER) for 12 weeks. The device consisted of a pulse generator and field generation via flat, flexible electric coils, that is, a mat the patients are asked to lie down on twice a day: soon after waking up in the morning and before bedtime. The patients were advised, as suggested by the manufacturer, to drink a glass of noncarbonated lukewarm water prior to the treatments in order to enhance treatment effects.

Figure 2 shows the general setup used for treatment application. The device produces a weak, low-frequency, pulsed electromagnetic field with a signal consisting of five series of pulses of half-wave-shaped sinusoidal variations. The pulse structure includes the sequences 1–5 as follows. Sequence 1: 0 μ T for 1–3 s; sequence 2: 3–12 μ T, a “base signal” for 12–16 s with a pulse frequency of 33.3 Hz (pulse width 30 ms); sequence 3: 30–150 μ T, an “additional signal” with a pulse width of 100–200 ms; sequence 4: sequences 2 and 3 are repeated 8–10 times; sequence 5: 0 μ T for 1–3 s. Amplitudes of the individual pulses within the sequence follow an exponential function with an arcuate pattern. After 2 min, the magnetic field changes its polarity [Gleim and Klopp, 2014]. For this study, the duration of signal sequences was set to a period of 8 min. The mat had six circular coils (diameter 14 cm) in two rows. The distance between rows was 30 cm from center to center of the coils. Longitudinally, the coils had distances 47 cm and 37 cm from each other. Since the coil geometry was very simple, the field distributions could be easily calculated. The current in the coil was adjusted to give a flux density of 50 μ T in the center of the coil and in the plane of the coil (approximately on the mat). According to the manufacturer, the maximum flux density (peak value) is about 50 μ T, which is roughly the same as the Earth's magnetic field. Graph (A) in Figure 3 shows the magnetic field as a function of distance from the mat along the axis of the coil, and graph (B) shows the variation of the flux density at a height of 5 cm from the mat. As can be seen, the field is practically localized within the area of the coils. Figure 4 shows the flux density map: the left edge is the axial symmetry axis (coil center), and outer radius of the coil is 70 mm. The border between the blue and greenish area corresponds to flux density, which is 50% of the flux density at the center of the coil.

Prior to the beginning of the study, the manufacturer labeled the devices as active or inactive, and the sealed code was given to only one investigator (SM) to be opened after the final statistical analyses. The active and inactive devices were identical in

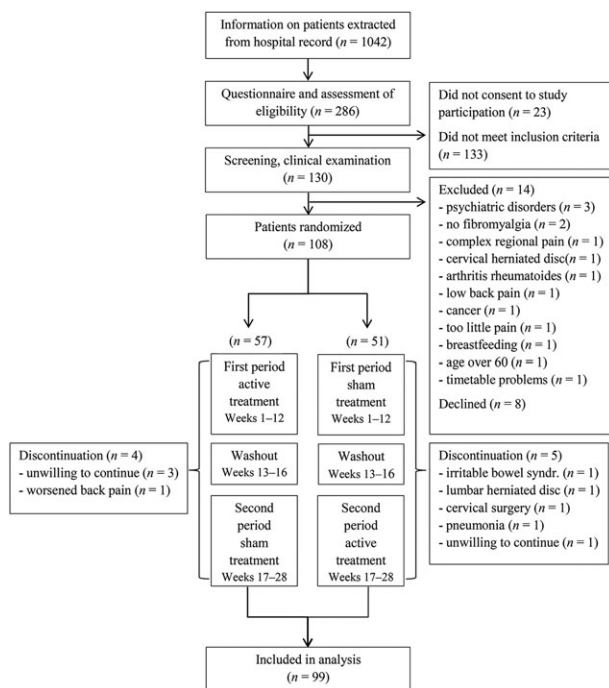


Fig. 1. Flow chart of the recruitment process and inclusion of participants.



Fig. 2. Treatment setup with the device comprising a pulse generator and mat for generating a pulsed electromagnetic field.

appearance, with sound and display indicator lights on during the setup and treatment. The handheld device with a light indicating that the magnetic field is on or off was removed from the package that was given to patients for therapy at home.

After the first treatment period in weeks 1–12, there was a washout period in weeks 13–16, during which there was no treatment and participants visited

the hospital in order to exchange the device for one labelled the opposite of what it had been during the first period, for a second treatment period in weeks 17–28. The participants kept a daily diary in which they recorded the actual application of the electromagnetic field therapy device and the use of drugs for the treatment of fibromyalgia symptoms.

Outcome Measures

Patients were evaluated at inclusion as well as at follow-up measurements after the first treatment period, the washout period, and second treatment period. The outcome measures were visual analog scale assessments of pain and stiffness of the past week ranging from 0 to 100 mm [McCormack et al., 1988]. In addition, all patients answered the Finnish version of the validated Fibromyalgia Impact Questionnaire (FIQ) [Gauffin et al., 2012]. The FIQ is a multidimensional self-administered questionnaire including 10 questions evaluating physical function, work status, depression, anxiety, sleep, pain, stiffness, fatigue, and well-being. The resulting score (FIQ total score), which indicates the impact of the disease on quality of life, ranged from 0 (no impact) to 100 (maximum impact) [Burckhardt et al., 1991]. We used the 10-item method for deriving a total score.

Sample Size

Before the study, the estimated sample size for power calculation was determined with the goal of measuring an improvement in the VAS pain score as found in a previous study of fibromyalgia populations [Sutbeyaz et al., 2009]. Power calculations indicated that a sample of 110 patients (55 in each treatment),

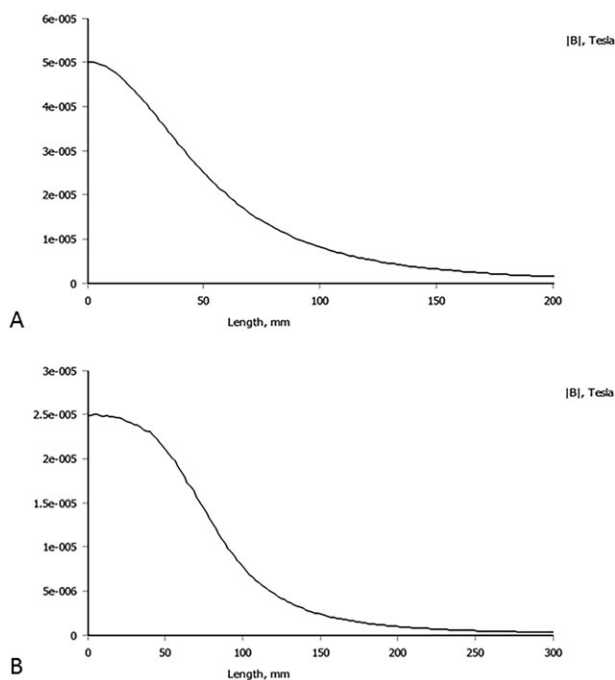


Fig. 3. Variation of the flux density at a height of 5 cm from the mat (A), and the magnetic field as a function of distance from the mat along the axis of the coil (B).

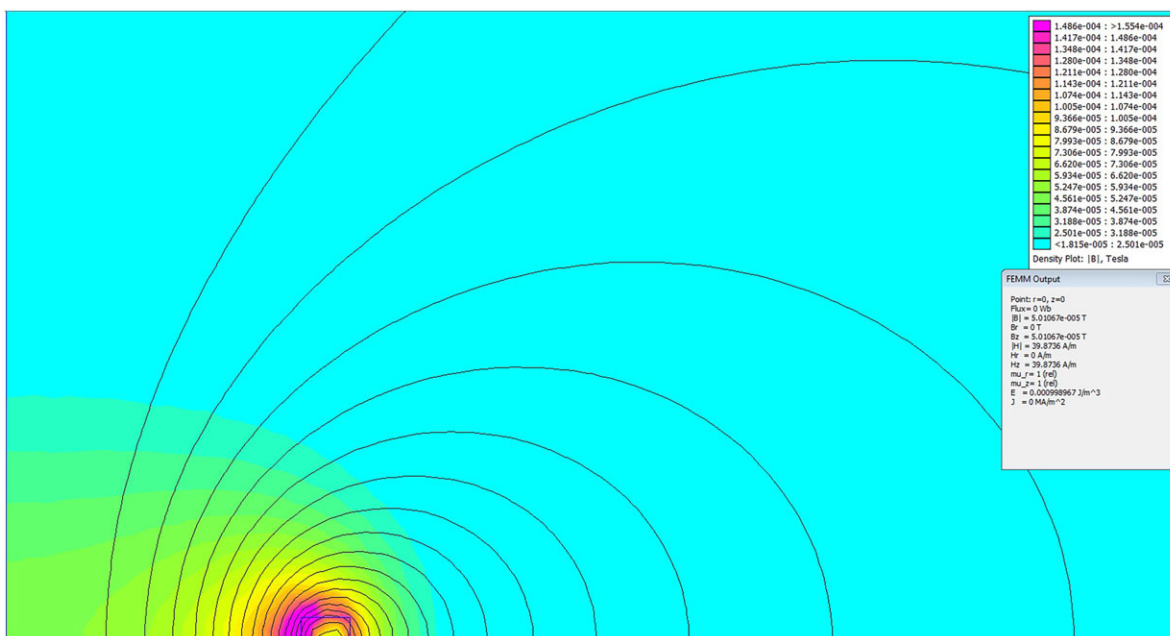


Fig. 4. The flux density distribution of the coil. The left edge is the axial symmetry axis (coil center) and the outer radius of the coil is 70 mm.

assuming a dropout rate of approximately 10%, would provide an 80% ($\beta = 0.20$) chance of detecting a 40% ($\alpha = 0.05$) difference in improvement between the active and sham treatments.

Statistical Analyses

Mean and standard deviations are given as descriptive statistics. The main outcome variables were analyzed according to the per-protocol analysis principle by using random effect models. The models were adjusted for period effect. The association between use of active and treatment devices and the changes in pain were examined with Pearson's correlation coefficient. The level of statistical significance was set at $\alpha \leq 0.05$. Data were analyzed using STATA 14.1 statistical software package (StataCorp, College Station, TX).

RESULTS

Study Population and Baseline Characteristics

Baseline demographic characteristics are presented in Table 1. The 108 patients had a mean age of 47 ± 10 (range 24–61) years and a mean body mass index of 29 ± 5 (range 18–44). The mean fibromyalgia illness duration, determined as the time since the fibromyalgia diagnosis, was 7 ± 7 (range 0–31) years. The most commonly used medications to treat or reduce the symptoms of fibromyalgia were analgesics.

Eighty-six patients (80%) were taking either prescription or over-the-counter analgesics at the beginning of the study. Ninety-two patients (85%) had one or more comorbidities. The most common comorbidities were different musculoskeletal problems such as osteoarthritis, spondylosis, and lower back pain (47%), lung and respiratory diseases (29%), cardiovascular diseases (22%), thyroid diseases (19%), neurological disorders (15%), mild mental disorders (12%), allergies (8%), and Type 1 or 2 diabetes (7%).

Dropout Rate and Harms

Of the 108 patients who started the treatments, nine dropped out during the study. Four patients dropped out during the active treatment period. The reasons were the following: worsened previous backache ($n = 1$) and unwilling to continue ($n = 3$). Five patients dropped out during the sham treatment period. The reasons for those dropouts were amplified overall pain and worsened irritable bowel syndrome ($n = 1$), lumbar herniated disc ($n = 1$), cervical herniated disc surgery ($n = 1$), chronic pneumonia ($n = 1$), and unwilling to continue ($n = 1$; Fig. 1). Of the enrolled patients, 92% completed the study.

Considering the harms of the study, one patient experienced an amplified overall pain sensation and had worsened irritable bowel syndrome during the sham treatment period. A 7-day treatment break was used as a cure. After continuing the treatment with the same sham device, the symptoms returned and the

TABLE 1. Demographic Characteristics of the Patients With Fibromyalgia

Variables	N=108
Age (years)	47 (10)
Height (cm)	164 (6)
Weight (kg)	77.6 (14.4)
Body mass index (kg/m ²)	28.9 (5.4)
Working status, n (%)	
Working	53 (49)
Not working	49 (45)
Retired	6 (6)
Time since fibromyalgia diagnosis (years)	7.1 (7.0)
Tender points score (0–18)	16.2 (1.9)
Beighton total score (0–9)	3.2 (2.8)
Pain, past week, VAS (0–100 mm)	70 (17)
Stiffness, past week, VAS (0–100 mm)	65 (22)
Sleep quality ^a , past week, VAS (0–100 mm)	33 (26)
Mood ^a , past week, VAS (0–100 mm)	29 (22)
Fibromyalgia Impact Questionnaire, total score (0–100)	52.4 (16.3)
Medications, n (%)	
Analgesics	86 (80)
Muscle relaxants	21 (19)
Antidepressants	49 (45)

Values are means (SD) or n (%).

^aNegative number indicates a lower quality of sleep or mood.

patient was withdrawn from the study. No adverse events occurred during the active treatment period.

Treatment Results

After the experiment, both active and sham treatment showed a significant improvement in pain, -12 , 95% CIs $[-18, -6]$ and -11 $[-17, -5]$ respectively; stiffness, -9 $[-15, -4]$ and -11 $[-17, -5]$; and FIQ -5 $[-8, -2]$ and -6 $[-9, -3]$. The baseline values and changes of pain, stiffness, and FIQ after treatments are given in Table 2. There were no significant differences at any of the outcome measures between active and sham treatments (Fig. 5).

Mean treatment compliance, measured as attendance at all 168 planned, 8-min treatment sessions, was 134 ± 41 (80%) when using the active devices and 131 ± 44 (78%) when using the sham devices. There was no correlation between the frequency of using the device and a decrease in pain, being $r = -0.11$, 95% CI $[-0.31, 0.10]$ in active treatments and $r = -0.10$, 95% CI $[-0.31, 0.12]$ in sham treatments.

DISCUSSION

To the best of our knowledge, this is the first randomized, double-blind, sham-controlled study to

examine the effect of low-energy PEMF treatment on pain, stiffness, and functional status in patients with fibromyalgia. The study showed that the treatment with an active device had no statistically significant improvement in pain, stiffness, or FIQ index over the sham treatment. All patients reported decreased pain, stiffness, and FIQ ratings across time, an occurrence describing the placebo effect. However, the reductions of pain and stiffness values in VAS, in the range of 9–12 mm, do not suggest clinical significance [Bird and Dickson, 2001]. By the end of the study, the patients still experienced severe pain and stiffness. Treatment was well tolerated and no serious side effects occurred. The treatment adherence was high (~80%).

Our finding is contrary to that of a previous RCT by Sutbeyaz et al. [2009] and a pilot study by Paolucci et al. [2016], showing that both PEMF and a non-pulsed magnetic field delivered by whole-body mats had beneficial effects on fibromyalgia patients' disease impact and pain intensity after somewhat short treatment periods. Instead, our finding is in line with another RCT by Alfano et al. [2001], who found no improvement from static magnetic sleep pads on functional status measured by FIQ, although active magnetic sleep pads decreased pain intensity significantly more than inactive pads did in the control group. However, the electromagnetic signals, dosage of the treatments, and study durations (three weeks in Sutbeyaz et al. [2009]; 4 weeks in Paolucci et al. [2016]; and 6 months in Alfano et al. [2001]) were different than those in the present study. In addition, the results of the above-mentioned previous studies should be interpreted with caution due to the small sample sizes in each treatment arm, which increases the possibility that positive results are due to chance.

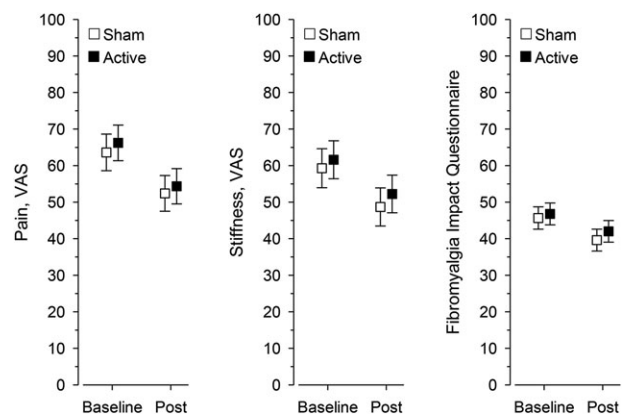


Fig 5. Changes in pain, stiffness, and Fibromyalgia Impact Questionnaire index after 12 weeks of treatments with active device and sham device. The square denotes mean and the bars denote 95% confidence intervals.

TABLE 2. Baseline, Change and Significance of Change Between Active and Sham Treatments

	Active		Sham		<i>P</i> *
	Baseline mean (SD)	Change mean (95%CI)	Baseline mean (SD)	Change mean (95%CI)	
Pain, VAS	66 (22)	-12 [-18, -6]	63 (22)	-11 [-17, -5]	0.88
Stiffness, VAS	61 (26)	-9 [-15, -4]	59 (25)	-11 [-17, -5]	0.77
FIQ	47 (15)	-5 [-8, -2]	45 (14)	-6 [-9, -3]	0.57

SD, standard deviation; CI, confidence interval; VAS, visual analog scale; FIQ, Fibromyalgia Impact Questionnaire.

*Adjusting for period effect.

However, some evidence has been found that exposure to electromagnetic fields affects pain sensitivity (nociception) and pain inhibition (analgesia) in some conditions [Del Seppia et al., 2007]. The inventors of the device used in this study suggest that functional improvements in microcirculation, lymphatic flow, and the immune system could stimulate local and higher homeostatic autoregulatory mechanisms [Gleim and Klopp, 2014]. However, from a physical point of view the effect of magnetic fields on human cells is via electromagnetic interaction. For static magnetic fields, only Lorentz force is relevant, that is, force acting on a moving charge. Time-varying magnetic fields induce voltages (induction). Principally, in both cases the primary mechanism is the same: relative movement of magnetic field lines and the organ in question. In this case, time-varying fields are used and the assumed effect is the generated voltage via induction. Time-varying magnetic field induces an electromotive force which is a voltage around a closed loop through which the time-varying magnetic flux goes. We can estimate the value of the induced electric field by taking a loop having an equal size than the coils ($r = 70$ mm) just above the coil and the amplitude of the flux density of $50 \mu\text{T}$ at a frequency of 100 Hz. This will give a peak value of 0.48 mV for the electromotive force, which corresponds to an electric field of 1 mV/m along the loop. Typically, electric potentials in a human body are some tens of millivolts and the corresponding distances from nanometers up to a millimeter. Even for a distance of 1 mm, the estimated electric field would mean a potential difference of $1 \mu\text{V}$. For neuron sizes, the induced potential difference would be several orders of magnitude less. Therefore, it is evident that a magnetic field equal to the Earth's magnetic field ($50 \mu\text{T}$) at frequencies $10\text{-}n \times 100$ Hz is too low to have clinically significant effects on a human body.

Regardless of the above-mentioned and assuming that PEMF therapy increases capillary blood flow in fibromyalgia, the question then arises of why passive therapy should be used to increase circulation,

as it may not have an effect on tissue metabolism and pain. It has been well established that exercise increases microcirculation and tissue metabolism [Shang et al., 2012], as well as having many other benefits for health issues that may be of great concern in patients with fibromyalgia. For instance, exercise improves muscle strength and endurance, can help in weight control, and improves mood and sleep [Kujala, 2009]. Active therapy modalities, such as land-based aerobic [Busch et al., 2007] and resistance exercise [Valkeinen et al., 2004; Busch et al., 2013] as well as aquatic training [Tomas-Carus et al., 2008], have been shown to improve function and relieve pain in patients with fibromyalgia, and currently exercise is recommended for the treatment of fibromyalgia in several international guidelines [Ablyn et al., 2013; Macfarlane et al., 2017]. The European League Against Rheumatism (EULAR), in their updated management recommendations, recently stated that exercise is the only dependable therapy for the treatment of fibromyalgia due to strong evidence for its effect on improvements in pain and physical function [Macfarlane et al., 2017].

This study has several strengths. First, we had a randomized double-blinded placebo-controlled treatment study with a long study duration. Second, all the patients, outcome assessors, and statistician were blinded to the treatment group assignment. Third, the sample size was large enough and the crossover design removed between patient variation [Yang and Stufken, 2008]. Fourth, considering that high dropout rates are a major issue with crossover design [Mills et al., 2009], in this study the dropout rate was low (8%) despite the relatively long duration of the study (28 weeks).

There are some limitations that might have influenced our study results. We used a crossover design despite some of its known disadvantages, specifically, period effect, and carryover effect [Altman, 1991]. These methodological flaws, however, were to some extent overcome in this study by statistically adjusting for the period effect, and by

counterbalancing the time between the first and second period sufficiently enough that the carryover effect was not assumed.

CONCLUSIONS

This study revealed that low-energy pulsed electromagnetic field treatment was no more effective than treatment with a sham device in reducing pain and stiffness or in improving functioning in women with fibromyalgia. Thus, pulsed electromagnetic field treatment cannot be recommended for treatment of fibromyalgia symptoms.

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REFERENCES

- Ablin J, Fitzcharles MA, Buskila D, Shir Y, Sommer C, Hauser W. 2013. Treatment of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines with special emphasis on complementary and alternative therapies. *Evid Based Complement Alternat Med*. 10.1155/2013/485272. Epub 2013 Nov 21. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3856149/> [Last accessed 2 March 2018].
- Alfano AP, Taylor AG, Foresman PA, Dunkl PR, McConnell GG, Conaway MR, Gillies GT. 2001. Static magnetic fields for treatment of fibromyalgia: a randomized controlled trial. *J Altern Complement Med* 7:53–64.
- Almeida TF, Roizenblatt S, Benedito-Silva AA, Tufik S. 2003. The effect of combined therapy (ultrasound and interferential current) on pain and sleep in fibromyalgia. *Pain* 104:665–672.
- Altman DG. 1991. *Practical statistics for medical research*. London, UK: Chapman and Hall. pp. 447–448.
- Bagnato GL, Miceli G, Marino N, Sciortino D, Bagnato GF. 2016. Pulsed electromagnetic fields in knee osteoarthritis: a double blind, placebo-controlled, randomized clinical trial. *Rheumatology (Oxford)* 55:755–762.
- Becker S, Schweinhardt P. 2012. Dysfunctional neurotransmitter systems in fibromyalgia, their role in central stress circuitry and pharmacological actions on these systems. *Pain Res Treat*: 741746. Available from: <http://www.hindawi.com/journals/prt/2012/741746/> [Last accessed 5 March 2018].
- Bird SB, Dickson EW. 2001. Clinically significant changes in pain along the visual analog scale. *Ann Emerg Med* 38:639–643.
- Bohn W, Hess L, Burger R. 2013. The effects of the “physical BEMER[®] vascular therapy”, a method for the physical stimulation of the vasomotion of precapillary microvessels in case of impaired microcirculation, on sleep, pain and quality of life of patients with different clinical pictures on the basis of three scientifically validated scales. *J Complement Integr Med* 10:S5–12, S5–13.
- Burckhardt CS, Clark SR, Bennett RM. 1991. The fibromyalgia impact questionnaire: development and validation. *J Rheumatol* 18:728–733.
- Burgmer M, Gaubitz M, Konrad C, Wrenger M, Hilgart S, Heuft G, Pfliegerer B. 2009. Decreased gray matter volumes in the cingulo-frontal cortex and the amygdala in patients with fibromyalgia. *Psychosom Med* 71:566–573.
- Busch AJ, Barber KA, Overend TJ, Peloso PM, Schachter CL. 2007. Exercise for treating fibromyalgia syndrome. *Cochrane Database Syst Rev* CD003786. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003786.pub2/full> [Last accessed 6 March 2018].
- Busch AJ, Webber SC, Richards RS, Bidonde J, Schachter CL, Schafer LA, Danyliw A, Sawant A, Dal Bello-Haas V, Rader T, Overend TJ. 2013. Resistance exercise training for fibromyalgia. *Cochrane Database Syst Rev* CD010884. Available from <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010884/full> [Last accessed 6 March 2018].
- Carbonario F, Matsutani LA, Yuan SL, Marques AP. 2013. Effectiveness of high-frequency transcutaneous electrical nerve stimulation at tender points as adjuvant therapy for patients with fibromyalgia. *Eur J Phys Rehabil Med* 49:197–204.
- Caro XJ, Winter EF. 2015. The role and importance of small fiber neuropathy in fibromyalgia pain. *Curr Pain Headache Rep* 19:55-015-0527-7.
- Choi DH, Kim HS. 2015. Quantitative analysis of nailfold capillary morphology in patients with fibromyalgia. *Korean J Intern Med* 30:531–537.
- Clauw DJ, Arnold LM, McCarberg BH, FibroCollaborative. 2011. The science of fibromyalgia. *Mayo Clin Proc* 86:907–911.
- Cuatrecasas G. 2009. Fibromyalgic syndromes: could growth hormone therapy be beneficial?. *Pediatr Endocrinol Rev* 6:529–533.
- Dailey DL, Rakel BA, Vance CG, Liebano RE, Amrit AS, Bush HM, Lee KS, Lee JE, Sluka KA. 2013. Transcutaneous electrical nerve stimulation reduces pain, fatigue and hyperalgesia while restoring central inhibition in primary fibromyalgia. *Pain* 154:2554–2562.
- Del Seppia C, Ghione S, Luschi P, Ossenkopp KP, Choleris E, Kavaliers M. 2007. Pain perception and electromagnetic fields. *Neurosci Biobehav Rev* 31:619–642.
- Gardner A, Boles RG. 2011. Beyond the serotonin hypothesis: mitochondria, inflammation and neurodegeneration in major depression and affective spectrum disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 35:730–743.
- Gauffin J, Hankama T, Kautiainen H, Arkela-Kautiainen M, Hannonen P, Haanpää M. 2012. Validation of a Finnish version of the fibromyalgia impact questionnaire (Finn-FIQ). *Scand J Pain* 3:15–20.
- Gleim P, Klopp R, inventors; Bemer International AG., assignee. Apparatus for stimulating local and higher homeostatic autoregulatory mechanisms in the organism. United States patent US 8, 808, 159 B2. 2014 Aug 19.
- Gracely RH, Petzke F, Wolf JM, Clauw DJ. 2002. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum* 46:1333–1343.
- Gupta A, Taly AB, Srivastava A, Kumar S, Thyloth M. 2009. Efficacy of pulsed electromagnetic field therapy in healing of pressure ulcers: a randomized control trial. *Neurol India* 57:622–626.
- Hug K, Rössli M. 2012. Therapeutic effects of whole-body devices applying pulsed electromagnetic fields (PEMF): a

- systematic literature review. *Bioelectromagnetics* 33: 95–105.
- Hussain SA, Al-Khalifa II, Andsim NA, Gorial FI. 2011. Adjuvant use of melatonin for treatment of fibromyalgia. *J Pineal Res* 50:267–271.
- Iran M, Zaffuto S, Bagnacani M, Annovi M, Moratti A, Cadossi R. 1990. Effect of low frequency pulsing electromagnetic fields on skin ulcers of venous origin in humans: a double-blind study. *J Orthop Res* 8:276–282.
- Kadetoff D, Lampa J, Westman M, Andersson M, Kosek E. 2012. Evidence of central inflammation in fibromyalgia-increased cerebrospinal fluid interleukin-8 levels. *J Neuroimmunol* 242:33–38.
- Klopp RC, Niemer W, Schmidt W. 2013. Effects of various physical treatment methods on arteriolar vasomotion and microhemodynamic functional characteristics in case of deficient regulation of organ blood flow. Results of a placebo-controlled, double-blind study. *J Complement Integr Med* 10:S39-46, S41-9.
- Kujala UM. 2009. Evidence on the effects of exercise therapy in the treatment of chronic disease. *Br J Sports Med* 43: 550–555.
- Lee JH, Cho KI, Kim SM, Lee HG, Kim TI. 2011. Arterial stiffness in female patients with fibromyalgia and its relationship to chronic emotional and physical stress. *Korean Circ J* 41:596–602.
- Li S, Yu B, Zhou D, He C, Zhuo Q, Hulme JM. 2013. Electromagnetic fields for treating osteoarthritis. *Cochrane Database Syst Rev* CD003523. Available from <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003523.pub2/full> [Last accessed 6 March 2018].
- Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Hauser W, Fluss E, Choy E, Kosek E, Amris K, Branco J, Dincer F, Leino-Arands P, Longley K, McCarthy GM, Makri S, Perrot S, Sarzi-Puttini P, Taylor A, Jones GT. 2017. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis* 76:318–328.
- Markov M. 2015. XXIst century magnetotherapy. *Electromagn Biol Med* 34:190–196.
- McCormack HM, Horne DJ, Sheather S. 1988. Clinical applications of visual analogue scales: a critical review. *Psychol Med* 18:1007–1019.
- Mills EJ, Chan AW, Wu P, Vail A, Guyatt GH, Altman DG. 2009. Design, analysis, and presentation of crossover trials. *Trials* 10:27-6215-10-27.
- Moldofsky H. 2010. Rheumatic manifestations of sleep disorders. *Curr Opin Rheumatol* 22:59–63.
- Morf S, Amann-Vesti B, Forster A, Franzeck UK, Koppensteiner R, Uebelhart D, Sprott H. 2005. Microcirculation abnormalities in patients with fibromyalgia—measured by capillary microscopy and laser fluxmetry. *Arthritis Res Ther* 7: R209–R216.
- Mutlu B, Paker N, Bugdayci D, Tekdos D, Kesiktas N. 2013. Efficacy of supervised exercise combined with transcutaneous electrical nerve stimulation in women with fibromyalgia: a prospective controlled study. *Rheumatol Int* 33: 649–655.
- Paolucci T, Piccinini G, Iosa M, Piermattei C, de Angelis S, Grasso MR, Zangrando F, Saraceni VM. 2016. Efficacy of extremely low-frequency magnetic field in fibromyalgia pain: a pilot study. *J Rehabil Res Dev* 53:1023–1034.
- Piecznik SR, Neustadt J. 2007. Mitochondrial dysfunction and molecular pathways of disease. *Exp Mol Pathol* 83:84–92.
- Sadreddini S, Molaefard M, Noshad H, Ardalan M, Asadi A. 2008. Efficacy of Raloxifen in treatment of fibromyalgia in menopausal women. *Eur J Intern Med* 19:350–355.
- Salazar AP, Stein C, Marchese RR, Plentz RD, Pagnussat AS. 2017. Electric stimulation for pain relief in patients with fibromyalgia: a systematic review and meta-analysis of randomized controlled trials. *Pain Physician* 20:15–25.
- Shang Y, Gurley K, Symons B, Long D, Srikuera R, Crofford LJ, Peterson CA, Yu G. 2012. Noninvasive optical characterization of muscle blood flow, oxygenation, and metabolism in women with fibromyalgia. *Arthritis Res Ther* 14:R236.
- Shupak NM, McKay JC, Nielson WR, Rollman GB, Prato FS, Thomas AW. 2006. Exposure to a specific pulsed low-frequency magnetic field: a double-blind placebo-controlled study of effects on pain ratings in rheumatoid arthritis and fibromyalgia patients. *Pain Res Manag* 11: 85–90.
- Sun J, Kwan RL, Zheng Y, Cheing GL. 2016. Effects of pulsed electromagnetic fields on peripheral blood circulation in people with diabetes: a randomized controlled trial. *Bioelectromagnetics* 37:290–297.
- Sutbeyaz ST, Sezer N, Koseoglu F, Kibar S. 2009. Low-frequency pulsed electromagnetic field therapy in fibromyalgia: a randomized, double-blind, sham-controlled clinical study. *Clin J Pain* 25:722–728.
- Thomas AW, Graham K, Prato FS, McKay J, Forster PM, Moulin DE, Chari S. 2007. A randomized, double-blind, placebo-controlled clinical trial using a low-frequency magnetic field in the treatment of musculoskeletal chronic pain. *Pain Res Manag* 12:249–258.
- Tomas-Carus P, Gusi N, Häkkinen A, Häkkinen K, Leal A, Ortega-Alonso A. 2008. Eight months of physical training in warm water improves physical and mental health in women with fibromyalgia: a randomized controlled trial. *J Rehabil Med* 40:248–252.
- Valkeinen H, Alen M, Hannonen P, Häkkinen A, Airaksinen O, Häkkinen K. 2004. Changes in knee extension and flexion force, EMG and functional capacity during strength training in older females with fibromyalgia and healthy controls. *Rheumatology (Oxford)* 43:225–228.
- Vincent A, Lahr BD, Wolfe F, Clauw DJ, Whipple MO, Oh TH, Barton DL, St Sauver J. 2013. Prevalence of fibromyalgia: a population-based study in olmsted county, minnesota, utilizing the Rochester epidemiology project. *Arthritis Care Res (Hoboken)* 65:786–792.
- Wolfe F, Anderson J, Harkness D, Bennett RM, Caro XJ, Goldenberg DL, Russell IJ, Yunus MB. 1997. Health status and disease severity in fibromyalgia: results of a six-center longitudinal study. *Arthritis Rheum* 40:1571–1579.
- Yang M, Stufken J. 2008. Optimal and efficient crossover designs for comparing test treatments to a control treatment under various models. *J Stat Plan Inference* 138:278–285.
- Yunus MB. 2007. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. *Semin Arthritis Rheum* 36:339–356.