Low-frequency Pulsed Electromagnetic Field Therapy in Fibromyalgia

A Randomized, Double-blind, Sham-controlled Clinical Study

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Objective: To evaluate the clinical effectiveness of low-frequency pulsed electromagnetic field (PEMF) therapy for women with fibromyalgia (FM).

Methods: Fifty-six women with FM, aged 18 to 60 years, were randomly assigned to either PEMF or sham therapy. Both the PEMF group (n = 28) and the sham group (n = 28) participated in therapy, 30 minutes per session, twice a day for 3 weeks. Treatment outcomes were assessed by the fibromyalgia Impact questionnaire (FIQ), visual analog scale (VAS), patient global assessment of response to therapy, Beck Depression Inventory (BDI), and Short-Form 36 health survey (SF-36), after treatment (at 4 wk) and follow-up (at 12 wk).

Results: The PEMF group showed significant improvements in FIQ, VAS pain, BDI score, and SF-36 scale in all domains at the end of therapy. These improvements in FIQ, VAS pain, and SF-36 pain score during follow-up. The sham group also showed improvement were maintained on all outcome measures except total FIQ scores after treatment. At 12 weeks follow-up, only improvements in the BDI and SF-36 scores were present in the sham group.

Conclusion: Low-frequency PEMF therapy might improve function, pain, fatigue, and global status in FM patients.

Key Words: fibromyalgia syndrome, chronic pain, pulsed electromagnetic fields, randomized clinical trial

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Fibromyalgia (FM) is a chronic pain disorder commonly seen in women and characterized by widespread muscle pain, tenderness, fatigue, nonrefreshing sleep, and other associated symptoms.[1,2] The etiology of FM is unknown and the pathogenesis is not clearly understood, but may involve abnormal levels of peripheral and central nervous system neurotransmitters, dysregulation of the hypothalamic-pituitary-adrenal axis,[3] or oxidative stress/nitric oxide.[4]

There is no standard treatment regimen for FM; therefore current therapy modalities are focused on relieving the symptoms of FM. Analgesics, antidepressants, and exercise are widely used to relieve the symptoms.[3,5,6] In the last decade, patient education, multidisciplinary group programs, and other nonpharmacologic interventions have become important aspects of FM therapy.[5,6] Thus, the use of a pulsed electromagnetic field (PEMF) represents an attractive alternative for patients with FM.

PEMF exposure is approved by the United States Food and Drug Administration for the treatment of problems associated with musculoskeletal disorders, including delayed-union or nonunion fractures, failed joint fusions, and congenital pseudoarthroses.[7–9] Specific joint disorders that have been investigated using this treatment modality include rheumatoid arthritis (RA),[10] osteoarthritis,[11,12] and rotator cuff tendonitis.[13] PEMF induces time-varying ionic currents in tissues, which stimulate changes in cellular calcium and cyclic adenosine monophosphate levels,[14] as well as in the synthesis of collagen, proteoglycans, DNA, and RNA.[15,16] In addition, some of the enzymes and hormones involved in skeletal homeostasis are affected by PEMF and it increases nitric oxide production and levels of reactive oxygen species.[17]

The pathophysiology that produces pain and disability in FM seems to involve a combination of central sensitization and nociceptive input. PEMF can alter pain perception and cognitive processing in both animals and humans. The effect of magnetic field exposure on pain behavior has been investigated in rats, mice, snails, pigeons, and humans.[18–20] Sartucci et al[21] examined the effect of weak, oscillating magnetic fields (MFs) exposure (constant-current rectangular pulses; 0.5 Hz, 0.1 ms in duration, 70 to 29 μT) on human pain perception and pain-related somatosensory evoked potentials (SEPs). After sham treatment, pain thresholds significantly increased, whereas after MFs a slight non-significant decrease in thresholds was found. After both treatments pain-related SEP amplitude was reduced, but this decrease was more evident and statistically significant only after MF exposure. The increase found in thresholds after sham exposure may be due to stress-induced analgesia, and the contrasting behavior recorded after MF exposure might indicate a suppression of stress-induced analgesia. The significant reduction in pain-related SEP amplitude observed after MF exposure provides the first evidence that human SEPs are influenced by MFs. Shupak et al[22] investigated the effect of PEMF exposure on pain and anxiety ratings in RA and FM populations. This study revealed a significant reduction in pain ratings from preexposure to postexposure for both RA and FM patients. These findings provide some initial support for the use of PEMF exposure to reduce pain in individuals with chronic pain. The aim of this study was to evaluate the efficacy of PEMF for the treatment of FM in a randomized, double-blind, sham-controlled trial.

MATERIALS AND METHODS

Participants

Sixty-eight patients with FM were recruited from the musculoskeletal rehabilitation outpatient clinic of the Ankara Physical Medicine and Rehabilitation Research

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Hospital. All participants were initially evaluated for the recruitment, based on an approved protocol. Screening included a medical and psychologic history, as well as physical and laboratory examinations. Criteria for study inclusion were: (1) fulfillment of American College of Rheumatology classification criteria for FM,[23] verified by rheumatologic examination: (a) widespread pain (axial plus upper and lower segment plus left and right side pain for ≥ 3 mo) and (b) tenderness at ≥ 11 of the 18 specific tender point sites; (2) patient-reported visual analog scale (VAS) scores for pain of ≥ 5 cm; (3) aged between 18 and 70 years; and (4) sufficient ability to understand the nature and potential risks of the study.

Exclusion criteria included ischemic heart disease, arrhythmia, uncontrolled thyroid disease, pregnancy, breastfeeding, cardiac pacemaker, malignancy, tuberculosis, neuropsychiatric disorders (dementia, cerebrovascular disease, alcohol abuse, severe depression, panic disorder, bipolar disorder, or psychosis), and comorbid painful conditions that could confuse the clinical picture, such as inflammatory arthritic conditions or cervical radiculopathy.

Participants had not received physical therapy or made changes in their pharmacologic therapy during the previous 2 months. No new drugs. No supplementary therapies, special diets, or aerobic exercise programs were allowed during the study period. Eight patients were excluded after the medical evaluation and 4 did not sign the consent form. Fifty-six patients with primary FM were studied.

All participants provided written informed consent. The study protocol was approved by the ethics committee of the Ankara Physical Medicine and Rehabilitation Research Hospital.

Randomization

After the baseline assessment and data collection, a computer-generated random number list was used to randomize patients into 2 equal groups, the PEMF or sham group. Randomization was performed using sequential sealed envelopes prepared by an independent physician before enrollment. The sealed envelopes contained a record of the allocation. The researchers and participants were all blind to the group allocation throughout the study.

PEMF Therapy

PEMF was administered to the whole body using a 1.8×0.6 m mat (wave ranger professional, MRS 2000+ Home, Eschestrasse 500, FL-9492 Eschen). This mat produced a PEMF with a mean intensity of 40 μT and frequency ranging from 0.1 to 64 Hz. Each patient lay on the mat for 30 minute per session, twice a day for 3 weeks. The sham intervention was identical to the actual intervention except that the PEMF device was not switched on. This method is particularly suitable for double-blind trials, as application of PEMF therapy does not cause any sensation in the patient. The device used had a specially designed switch concealed at the back that enabled the independent researcher to interrupt the PEMF for the sham group; the "on" sign and the parameters of PEMF therapy were displayed to all patients (sham and PEMF groups) throughout the procedure.

Assessment

All patients were assessed at baseline, at the end of therapy, and after 12 weeks, by the same assessor, who was blinded to treatment. Whenever possible, follow-up was conducted at the same time of day as the baseline assessment, to control for diurnal fluctuation. At each assessment, pain severity was measured on a 100 mm VAS. Both groups completed the Fibromyalgia Impact Questionnaire (FIQ), the Short-Form 36 Health Survey (SF-36), and the Beck Depression Inventory (BDI) at baseline, at the end of therapy, and at the follow-up. In addition, at the end of therapy and after 12 weeks, both the PEMF and sham group responded to the Patient Global Assessment of Response to Therapy (PGART).

Primary Outcome Measures

FIQ

FM-related quality of life was assessed by a validated Turkish version of the FIQ.[24] The FIQ is a 20-item, patient-reported instrument, developed by Burckhardt and coworkers.[25] It consists of 10 subscales, which are combined to yield a total score. Eleven questions are specifically related to physical functioning (PF). The remaining items assess pain, fatigue, stiffness, tiredness on waking, difficulty in working, days when the patient feels good, and symptoms of anxiety and depression. Scores range from 0 to 100, with higher scores signifying greater disease impact. The FIQ is responsive to change and has been translated into many languages.

VAS

The VAS was used to assess subjective pain intensity.[26,27] Patients marked the extent of pain they had experienced during the previous week on a horizontal 100 mm VAS (0 = no pain and 100 = the worst imaginable).

Secondary Outcome Measures

PGART

One of the secondary outcome measures was the patient's global assessment of their impression of improvement. The question asked was "What were the effects of treatment on your complaints?" Patients indicated their answers on a 5-point Likert scale (1 = much better, 2 = better, 3 = slightly better, 4 = no change, and 5 = worse).

BDI

All patients evaluated filled out the BDI, self-reported scale, which evaluates 21 symptoms of depression. For each symptom, patients rate themselves as 0, 1, 2, or 3. The maximum score is 63 and the minimum score is 0. Higher scores indicate greater depression.[28,29]

SF-36 Health Survey

The Medical Outcomes Study SF-36 questionnaire (Turkish version) was used to measure quality of life.[30] The SF-36 includes 1 multi-item scale that assesses 8 health concepts: PF, role limitations-physical, bodily pain, general health (GH), vitality, social functioning, role limitations-emotional, and mental health. SF-36 scale scores derive from 2 summary measures of health status: the physical component summary (PCS) and mental component summary (MCS). The PCS includes scales assessing PF, role limitations-physical, bodily pain, and GH. The MCS includes scales assessing vitality, social functioning, role limitations-emotional, and mental health. Each SF-36 scale is scored using norm-based methods that standardize the scores to a mean of 50 and a SD of 10 in the general population, with higher scores indicating better health.

Scores on the 8 SF-36 scales were further aggregated to produce PCS and MCS scores, which are also measures of health status. The PCS and MCS were also scored using norm-based methods.[31] The validity and reliability study of the Turkish version of SF-36 has been well documented.[32]

Sample Size

The required sample size was determined with a goal of measuring an improvement in VAS pain score with a SD of 2.0, as found in previous studies of FM populations.[32] Power calculations indicated that a sample of 40 patients would provide an 80% ($\beta = 0.20$) chance of detecting a 20% ($\alpha = 0.05$) difference in improvement between the groups.

Statistical Analysis

An intention-to-treat analysis was performed using the last-observation-carried-forward method. The level of significance was set at $P < 0.05$ (2-tailed tests). Groups were compared at baseline using the t test for independent samples for the continuous variables, and the χ^2 test for categorical data. As all outcome variables were normally distributed, analysis of variance with repeated measures was chosen to test the research hypothesis, with a between-patient factor at 2 levels (the 2 groups) and a within-patient factor at 3 levels (assessment time: pretreatment, post-treatment, and follow-up). Independent sample t tests were used to compare the change of scores at treatment completion. A 95% confidence interval (95% CI) was used. The P values and CIs from the comparisons of the means were shown with Bonferroni correction.

To analyze PGART, a score of 1 or 2 was considered clinically important; all other scores and missing values from patients who dropped out, were computed as nonresponsive to treatment. Fisher exact test and the χ^2 test were used to determine differences in rates of improvement between the 2 groups. Data were analyzed using SPSS for Windows, version 11.5 (Chicago, IL).

RESULTS

Demographic Data

A total of 68 patients were screened for inclusion in the study. Of these, 56 patients were enrolled in the study and randomized to 1 of 2 treatment groups: PEMF therapy (28 patients) or sham therapy (28 patients). At baseline, no significant differences were present among the groups regarding age, body mass index, year of education, socio-economic status, disease duration, or total FIQ score. However, the antidepressant intake was higher in the sham group. Mean ages were similar between the groups, and ages ranged from 23 to 60 years. The duration of FM ranged from 2.0 to 6.5 years. The demographics of the study patients are summarized in Table 1.

TABLE 1. Baseline Characteristics of the Study Patients*

	PEMF Group (n = 28)	Sham PEMF Group (n = 28)	P
Age, mean ± SD (y)	42.96 ± 9.57	40.89 ± 6.88	0.35
Body mass index, mean ± SD (y)	25.56 ± 7.16	25.48 ± 4.21	0.96
Duration of FM, mean ± SD (y)	5.6 ± 4.3	5.9 ± 6.0	0.84
Education, %			0.75
< 8 y	78.6	85.7	
8–12 y	14.3	7.1	
> 12 y	7.1	7.1	
Marital status, %			0.75
Unmarried	21.4	25.0	
Married	78.6	75.0	
Work status, %			0.75
Homemaker	75.0	78.6	
Working	25.0	21.4	
Concomitant medications, %			0.35
NSAID	21.4	25.0	
Tricyclic antidepressants	7.1	14.3	
SSRIs	10.7	25.0	
Anxiolytics	3.6	0	
Muscle relaxants	3.6	3.6	
Antiepileptics	3.6	0	
FIQ (total) score, mean ± SD	66.0 ± 12.8	61.9 ± 14.7	0.28
Physical functioning	5.82 ± 1.99	5.11 ± 1.43	
Number of days felt good	7.35 ± 2.09	5.26 ± 1.90	
Ability to do job	7.25 ± 2.10	6.60 ± 2.33	
Pain	7.46 ± 1.97	7.25 ± 1.81	
Fatigue	8.42 ± 1.85	8.82 ± 1.94	
Morning tiredness	8.78 ± 2.42	9.03 ± 1.83	
Stiffness	8.28 ± 2.40	6.14 ± 2.23	
Anxiety	7.14 ± 3.30	8.78 ± 1.59	
Depression	7.28 ± 3.12	7.85 ± 1.60	

*P values were determined by Student's t test or χ^2 test for categorical data.

FIQ indicates Fibromyalgia Impact Questionnaire; FM, fibromylagia; NSAIDs, nonsteroidal anti-inflammatory drugs; PEMF, pulsed electromagnetic field; SSRIs, selective serotonin reuptake inhibitors.

Dropout Rate

Figure 1 shows the flowchart for the study. At the end of 12 weeks, 45 patients were still participating in the study protocol. During the study, 11 patients dropped out: 5 from the PEMF group and 6 from the sham group. The reasons were: no benefit from PEMF or sham treatment (n = 2 and n = 5, respectively), temporary orthostatic hypotension after PEMF treatment (n = 2), death of father (n = 1), and stress at home (n = 1). Seventy-five percent of enrolled patients completed the study, with no significant differences in dropout rates (82.1% and 78.6% in the PEMF and sham groups, respectively).

Efficacy Results

The FIQ scores in the PEMF group showed significant improvements at the end of therapy (fourth week) compared with baseline. The PEMF group had a significantly lower FIQ score than the sham group at the end of therapy. The mean ± SEM change in the FIQ score from baseline to therapy end was -33.51 ± 2.71 (52%) in the PEMF group and -8.65 ± 1.91 (11%) in the sham group, with a between-group difference of -25.46 (95% CI -32.11, -18.80) ($P = 0.000$) (Tables 2, 3; Fig. 2). A significant difference was also observed between the groups at follow-up ($P = 0.000$). PEMF therapy significantly improved VAS pain scores at the end of therapy (Table 2). In the PEMF group, 13 patients achieved 30% improvement, whereas 8 patients achieved 50% improvement on the VAS score after treatment. At follow-up, 6 of the patients in the PEMF group achieved 30% improvement on the VAS scores. In the sham group, 3 patients achieved 30% improvement on the VAS scores after treatment.

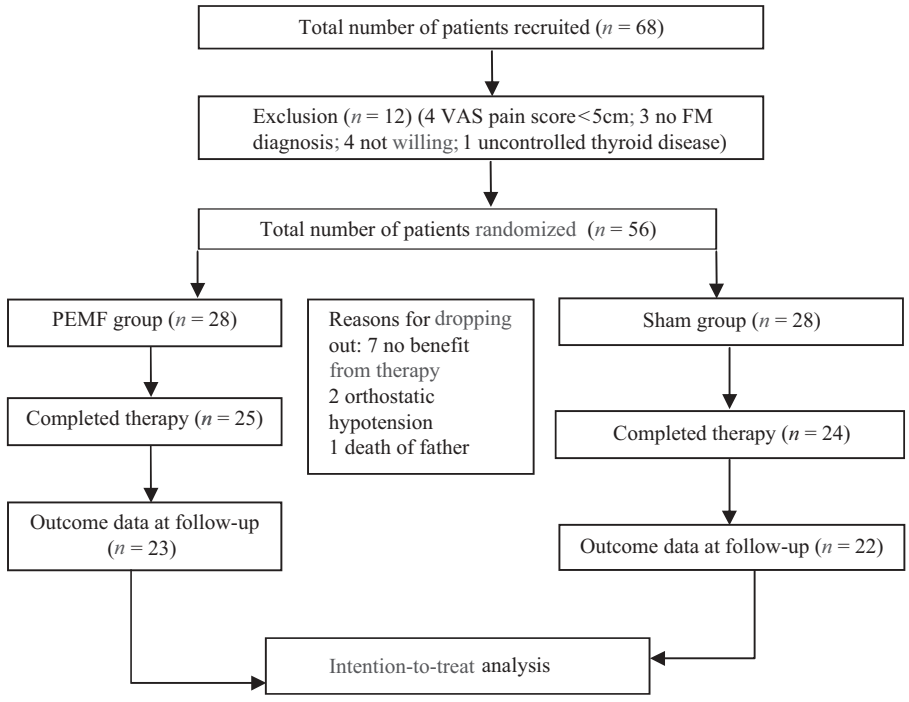

FIGURE 1. Flow diagram for randomized patient assignment. FM indicates fibromyalgia; PEMF, pulsed electromagnetic field; VAS, visual analog scale.

Sixty-four percent of patients from the PEMF group rated themselves as clinically improved after treatment, but 54% of the PEMF patients reported worsening in the PGART at the follow-up. Twenty-one percent of sham patients were responders after treatment and showed no further improvement at the follow-up. There was a significant difference between the groups after treatment ($P = 0.018$), but not at follow-up ($P = 0.538$).

The BDI score at each of the 2 assessment time points showed improvement from baseline in the sham group, but in the PEMF group the BDI scores were only improved after treatment. However, the improvements were not significantly different between 2 groups (Table 3).

Table 3 shows the statistically significant differences in SF-36 pain score from baseline observed in both groups at each of the 2 assessment time points. In all domains except GH, changes in the SF-36 scores from baseline to the end of therapy showed a trend towards greater improvement in both groups.

Side-effects

Two patients in the PEMF group had orthostatic hypotension and were withdrawn from the study. Orthostatic hypotension did not continue after stopping PEMF treatment.

TABLE 2. Result of the FIQ, VAS Pain, BDI, SF-36 Score Outcome Measures After Treatment

	PEMF Group (n = 25)	Sham Group (n = 24)	Between-group Difference at	
	Change, Mean ± SEM	Change, Mean ± SEM	Endpoint (95% CI)	*P*
FIQ total score (range: 0-80)	− 33.51 ± 2.71	− 8.65 ± 1.91	− 25.46 (− 32.11, − 18.80)	0.000
VAS pain (range: 0-100 mm)	− 35.29 ± 2.18	− 4.98 ± 1.28	− 30.31 (− 35.38, − 25.23)	0.000
BDI total score (range: 0-63)	− 4.84 ± 1.52	− 2.33 ± 0.37	− 2.50 (− 5.71, 0.70)	0.123
SF-36 (range: 0-100)				
Physical functioning	13.69 ± 1.13	0.72 ± 0.45	12.96 (10.46, 15.46)	0.000
Role limitations-physical	8.73 ± 1.53	1.15 ± 1.17	7.58 (3.66, 11.50)	0.000
Bodily pain	10.33 ± 1.06	1.68 ± 0.53	8.64 (6.21, 11.07)	0.000
General health	1.04 ± 0.92	0.60 ± 0.49	0.44 (− 1.69, 2.58)	0.679
Vitality	11.95 ± 1.74	3.07 ± 0.42	8.87 (5.19, 12.55)	0.000
Social functioning	12.53 ± 1.20	3.81 ± 0.94	8.71 (5.62, 11.81)	0.000
Role limitations-emotional	13.58 ± 2.11	2.26 ± 1.14	11.32 (6.43, 16.21)	0.000
Mental health	14.89 ± 1.39	3.53 ± 0.99	11.35 (7.87, 14.82)	0.000

BDI indicates Beck Depression Inventory; CI, confidence interval; FIQ, Fibromyalgia Impact Questionnaire; PEMF, pulsed electromagnetic field; SF-36, Short-Form 36; VAS, visual analog scale.

TABLE 3. Changes of Outcome Parameters at Pretreatment, Posttreatment, and Follow-up (Intention-to-treat Analysis)

	n	Baseline	After Treatment	Follow-up
FIQ				
PEMF group	28	66.0 ± 12.8	32.5 ± 14.2**	54.8 ± 14.2**
Sham group	28	61.9 ± 14.7	53.9 ± 12.6**	61.2 ± 13.7
VAS pain				
PEMF group	28	73.3 ± 14.0	38.07 ± 16.9**	59.4 ± 9.8**
Sham group	28	68.4 ± 12.1	63.4 ± 13.8**	67.4 ± 11.8
BDI				
PEMF group	28	39.9 ± 7.5	35.2 ± 16.8*	37.5 ± 15.4
Sham group	28	28.0 ± 13.6	25.6 ± 12.6**	27.1 ± 13.1**
SF-36 pain score				
PEMF group	28	32.0 ± 3.9	42.7 ± 4.4**	32.6 ± 3.3**
Sham group	28	32.3 ± 7.7	33.9 ± 8.1*	31.7 ± 7.3*

Data are mean ± SD. *P* values were obtained using analysis of variance for repeated measures (with Bonferroni correction).

*$P < 0.01$; **$P < 0.001$.

BDI indicates Beck Depression Inventory; FIQ, Fibromyalgia Impact Questionnaire; PEMF, pulsed electromagnetic field; SF-36, Short-Form 36; VAS, visual analog scale.

DISCUSSION

To the best of our knowledge, this is the first randomized, double-blind, sham-controlled study to examine the effect of PEMF therapy in patients with FM. This 12-week trial showed that low-frequency PEMF therapy has beneficial effects in terms of function, pain, fatigue, and global status in patients with FM.

Patients in both the PEMF and sham therapy groups experienced improvement in all outcome measures after treatment. The PEMF group showed significant beneficial effects in FIQ, VAS pain, BDI, and SF-36 pain scores at the end of therapy. The sham group also showed improvement in all outcome measures in the same period.

At the end of therapy, the difference between groups was in favor of PEMF therapy in all outcome measures except the SF-36 GH domain and BDI scores.

In the PEMF group, all the outcomes of the study except BDI scores continued to improve up to week 12. The improvements of the primary outcomes (FIQ, VAS pain) in the sham group were not sustained 12 weeks after treatment ended. However, in this group, only the BDI and SF-36 pain scores were continued until the follow-up.

Shupak et al[22] studied the efficacy of an acute 30-minute MF exposure on pain and anxiety in female RA (n = 13) and FM patients (n = 18) who received either a PEMF or sham-exposure treatment. They found that patients in the PEMF group for both patient populations had significantly reduced VAS scores; however, of the sham-exposed patients, only those in the FM sample had significantly reduced scores. They suggested that, aside from the placebo effect, decreases in pain ratings for patients randomly assigned to the sham group can be attributed to relaxation from being seated in a comfortable chair for 55 minutes during therapy. In this study, the improvements seen in the sham group could be placebo or regression to the mean or reflect the natural history of the disease.[33]

Dunkl and colleagues[34] found that the FIQ was the measure that was most responsive to perceived clinical improvement, and they recommended its inclusion as a primary end point in FM clinical trials. In this study, PEMF significantly improved the FIQ total score. It has been shown that PGART can discriminate treatment effects in FM.[3] We observed that over 64% of completers in the PEMF therapy group reported an improvement in their overall status, whereas only 14% reported worsening. In the sham arm, the most frequent category reported was ''worsening,'' with over 53% of sham patients who completed the trial rating themselves as worse. Low-frequency PEMF may improve many of the symptoms of FM, which is reflected in this outcome measure.

PEMF application was generally well tolerated in this study. There were no treatment-related serious adverse events reported by the patients. Two patients experienced orthostatic hypotension that stopped when treatment was discontinued. There have been no previous reports of orthostatic hypotension during low-frequency PEMF treatment in the literature. In addition, this method of PEMF application can be used easily at home in the treatment of patients with FM.

The clinical rationale for using PEMF therapy for patients with FM is primarily based on empirical observations and interpretation of information from physiologic and clinical studies. Several factors might mediate therapeutic effects, such as alteration in pain perception, increasing pain thresholds and hormone levels, inhibition of inflammatory edema, and vascular changes.[35]

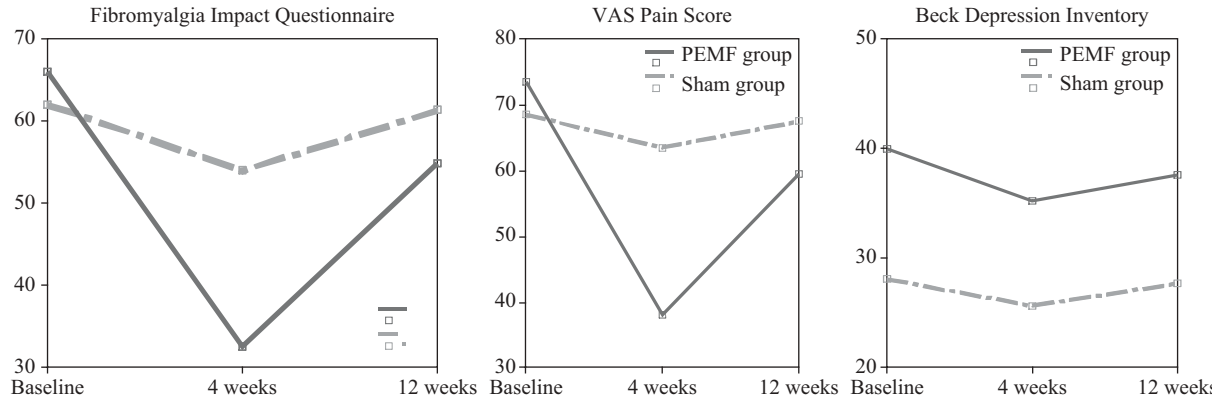

FIGURE 2. Changes in the fibromyalgia impact questionnaire, visual analog scale (VAS) pain, and Beck Depression Inventory, Short Form-36 pain score. PEMF indicates pulsed electromagnetic field.

Antidepressants are widely used to treat symptoms associated with FM.[36–38] Although more trials are needed to explore the efficacy of antidepressants in FM, the evidence supports the use of antidepressants in treating pain and other symptoms associated with the disorder.[39] In this study, despite the fact that antidepressant intake was higher in the sham group; no difference was found between the study groups in baseline pain and disease activity scores. However, the higher antidepressant intake in the sham group might positively affect outcome scores, and this may, therefore, be regarded as a potential limitation of the study. Although the PEMF therapy showed improvements in all postintervention outcomes except BDI scores, and this continued during the follow-up period, at 12 weeks a regression of the beneficial effects of PEMF therapy was observed, compared with the values after treatment. Thus, from our results, it seems that the PEMF therapy provided short-term improvement, and this was supported by the PGART scores of patients at follow-up.

As we have previously stated, the PEMF affect pain perception in many different ways. These actions are both direct and indirect. Therefore, we suggest that longer treatment times may lead to better clinical results.

Shupak et al[22] are the only researchers to have investigated the effect of PEMF on pain ratings in FM patients in a randomized clinical trial, so there is no widely accepted agreement on the optimal duration or technique of application. This is another potential limitation to our study. Also, only women were entered in this study, which may not be representative of all FM patients. Further research is needed to optimize the duration and application of PEMF treatment, as well as to identify the mechanisms of treatment action in FM.

The findings of this study support the need for future investigations of PEMF therapy for the treatment of FM. Such studies should explore the duration of the effects of PEMF by performing longer-term follow-up evaluations, and also by using different parameters of stimulation. In conclusion, PEMF therapy may improve function, pain, fatigue, and global status in FM patients and may offer a potential therapeutic adjunct to current FM therapies in the future.

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