

## Randomized, prospective, and controlled clinical trial of pulsed electromagnetic field stimulation for cervical fusion

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Received 17 July 2006; accepted 11 June 2007

### Abstract

**BACKGROUND CONTEXT:** Multilevel fusions, the use of allograft bone, and smoking have been associated with an increased risk of nonunion after anterior cervical discectomy and fusion (ACDF) procedures. Pulsed electromagnetic field (PEMF) stimulation has been shown to increase arthrodesis rates after lumbar spine fusion surgery, but there are minimal data concerning the effect of PEMF stimulation on cervical spine fusion.

**PURPOSE:** To determine the efficacy and safety of PEMF stimulation as an adjunct to arthrodesis after ACDF in patients with potential risk factors for nonunion.

**STUDY DESIGN:** A randomized, controlled, prospective multicenter clinical trial.

**PATIENT SAMPLE:** Three hundred and twenty-three patients with radiographic evidence (computed tomography-myelogram [CT-myelo] or magnetic resonance imaging [MRI]) of a compressed cervical nerve root and symptomatic radiculopathy appropriate to the compressed root that had failed to respond to nonoperative management were enrolled in the study. The patients were either smokers (more than one pack per day) and/or were undergoing multilevel fusions. All patients underwent ACDF using the Smith–Robinson technique. Allograft bone and an anterior cervical plate were used in all cases.

**OUTCOME MEASURES:** Measurements were obtained preoperatively and at each postoperative interval and included neurologic assessment, visual analog scale (VAS) scores for shoulder/arm pain at rest and with activity, SF-12 scores, the neck disability index (NDI), and radiographs (anteroposterior, lateral, and flexion–extension views). Two orthopedic surgeons not otherwise affiliated with the study and blinded to treatment group evaluated the radiographs, as did a blinded radiologist. Adverse events were reported by all patients throughout the study to determine device safety.

FDA device/drug status: FDA-approved (Cervical Stim, Ortho fix, Inc.). Nothing of value received from a commercial entity related to this manuscript.

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**METHODS:** Patients were randomly assigned to one of two groups: those receiving PEMF stimulation after surgery (PEMF group, 163 patients) and those not receiving PEMF stimulation (control group, 160 patients). Postoperative care was otherwise identical. Follow-up was carried out at 1, 2, 3, 6, and 12 months postoperatively.

**RESULTS:** The PEMF and control groups were comparable with regard to age, gender, race, past medical history, smoking status, and litigation status. Both groups were also comparable in terms of baseline diagnosis (herniated disc, spondylosis, or both) and number of levels operated (one, two, three, or four). At 6 months postoperatively, the PEMF group had a significantly higher fusion rate than the control group (83.6% vs. 68.6%,  $p=.0065$ ). At 12 months after surgery, the stimulated group had a fusion rate of 92.8% compared with 86.7% for the control group ( $p=.1129$ ). There were no significant differences between the PEMF and control groups with regard to VAS pain scores, NDI, or SF-12 scores at 6 or 12 months. No significant differences were found in the incidence of adverse events in the groups.

**CONCLUSIONS:** This is the first randomized, controlled trial that analyzes the effects of PEMF stimulation on cervical spine fusion. PEMF stimulation significantly improved the fusion rate at 6 months postoperatively in patients undergoing ACDF with an allograft and an anterior cervical plate, the eligibility criteria being patients who were smokers or had undergone multilevel cervical fusion. At 12 months postoperatively, however, the fusion rate for PEMF patients was not significantly different from that of the control group. There were no differences in the incidence of adverse events in the two groups, indicating that the use of PEMF stimulation is safe in this clinical setting. © 2008 Elsevier Inc. All rights reserved.

*Keywords:*

Pulsed electromagnetic field (PEMF) stimulation; Anterior cervical fusion; Allograft; Multilevel; Smoking

## Introduction

Most research regarding the use of pulsed electromagnetic field (PEMF) stimulation as an adjunct to spinal fusion has been related to lumbar arthrodesis. Fusion rates in the lumbar spine with the adjunctive use of PEMF stimulation have been reported to range from 92.2% to 97.9% [1–3]. There is a paucity of literature that addresses the use of PEMF stimulation in the cervical spine. In a retrospective, single-center case series, Shen et al. demonstrated a 95% arthrodesis rate with the use of PEMF stimulation in instrumented, multilevel anterior and posterior cervical fusions [4]. To date, however, there have been no randomized, controlled clinical trials that investigate the use of PEMF stimulation as an adjunct to cervical spine fusion.

The purpose of this study was to determine the efficacy and safety of PEMF stimulation as an adjunct to anterior cervical discectomy and fusion (ACDF) via a prospective, multicenter, randomized, and controlled clinical trial. Prior research has identified the use of allograft bone [5,6], multilevel fusion [7,8], and a history of smoking [9] to be risk factors for nonunion after ACDF. Also, allograft interbody implants and anterior plates are increasingly used for this procedure. These factors were incorporated into the study design.

## Material and methods

This was a prospective, multicenter, randomized, and controlled clinical trial of the efficacy and safety of PEMF stimulation in patients undergoing ACDF. The research was carried out under the auspices of the US Food and Drug

Administration as an Investigational Device Exemption study of a PEMF device designed specifically for cervical spine use (Cervical-Stim; Orthofix Inc., McKinney, TX). Patients who met the inclusion/exclusion criteria were randomized to receive PEMF stimulation or no stimulation after surgery. Anterior cervical plates and allograft interbody implants were used in all patients. Fusion efficacy was assessed through comparative radiographic analysis, whereas safety was analyzed using a comparative, statistical evaluation of adverse effects.

### *Inclusion/exclusion criteria*

Men and women aged 18 to 75 years were included. All participants had evidence of nerve root compression based on computed tomography-myelogram or magnetic resonance imaging. Cervical spine levels included in this study were C3–C4 to C7–T1. Each patient had symptomatic radiculopathy correlative to the radiographically compressed level(s). Further, each subject had a visual analog scale (VAS) pain score greater than or equal to 5, and/or upper extremity weakness at the correlative level. To be eligible for the trial, all patients had to be active smokers (more than one pack of cigarettes per day) or be undergoing multilevel ACDF.

Exclusion criteria included a pertinent history of trauma, previous posterior cervical approach or revision surgery, systemic conditions (ie, cancer, renal disease/dysfunction, poorly controlled diabetes, or steroid use), and regional conditions (ie, Paget's disease or spondylitis). Other criteria barring participation were a history of systemic or local infection (within 2 weeks of surgery), migraine headaches, seizure disorder, or neurological disease or injury. Patients

with incompetent immune systems were also excluded, as were those with cardiac pacemakers, defibrillators, direct current stimulator implants, cochlear implants, or cranial stimulators. Finally, women who were planning (within 12 months) a pregnancy or were pregnant or nursing were not included in this study.

#### Baseline and follow-up parameters

The study was approved by the institutional review boards at each participating site. Once patients were enrolled in the study and appropriate informed consent had been obtained, they were randomly assigned to one of two surgical groups: those who received PEMF stimulation and those who did not. Each patient underwent an ACDF via a Smith–Robinson technique with the use of allograft bone and the Atlantis Anterior Cervical Plate System (Medtronic Sofamor Danek, Memphis, TN).

Baseline and follow-up evaluations were identical for both groups. All patients had preoperative history reviews and physical examinations and a neurological assessment. Baseline assessments of pain were done using the VAS, and were repeated at 6 and 12 months postoperatively. The SF-12, a validated measurement of physical health, and the (NDI), a functional assessment, were performed at the same intervals.

Postoperative care for both groups was identical. All patients wore a soft cervical collar for 1 week postoperatively. Those randomized to the PEMF stimulation group started within 7 days postoperatively and wore the Cervical-Stim device for 4 hours per day for 3 months (Fig. 1). Follow-



Fig. 1. The Cervical-Stim device.

up visits occurred at 1-, 2-, 3-, 6-, and 12-month intervals. Compliance was assessed at each postoperative visit via a printout of PEMF stimulation “on” time, which was automatically monitored by the Cervical-Stim device. Radiographic examinations, including anteroposterior, lateral, and flexion/extension lateral images, were performed at 3, 6, and 12 months postoperatively. The safety of PEMF stimulation was assessed by a thorough analysis of both anticipated and unanticipated adverse events occurring in both groups.

#### Fusion analysis

All films were digitized for post hoc consensus review. Two independent orthopedic surgeons read all films in a blinded fashion. In the event of conflicting analyses, a blinded radiologist also assessed the films. Levels that were deemed to be fused had 1) greater than or equal to 50% bony bridging through both surfaces of the graft–vertebra interface, 2) no radiolucency at any portion of the graft–vertebra junction, and 3) less than or equal to four degrees of motion between adjacent fused vertebrae. The motion assessment was performed using a customized software package (QMA; Medical Metrics, Inc., Houston, TX) that produced a digitized overlay of the flexion and extension views. Only patients with arthrodesis at all operated levels were considered “fused” in this study.

#### Statistical analysis

Pearson chi-square test was used to assess statistically significant differences in fusion outcomes between the groups at 6 and 12 months. The Mantel–Haenszel chi-square test was used to adjust for demographic variables.

## Results

#### Baseline and demographic data

The demographics of the 323 patients included in the study are shown in Table 1. There were no statistically

Table 1  
Patient demographics

Variables	Control (N=160)	PEMF (N=163)
Age (y)	46.7 (26–72)	46.9 (24–73)
Male	85 (53.1%)	90 (55.2%)
Race		
Caucasian	150 (93.8%)	151 (92.6%)
African-American	7 (4.4%)	10 (6.1%)
Hispanic	3 (1.9%)	2 (1.2%)
Worker's compensation	35 (21.9%)	41 (25.2%)
Litigation	7 (4.4%)	9 (5.5%)
Smoking status		
Smoking	79 (49.4%)	80 (49.1%)
Nonsmoking	81 (50.6%)	83 (50.9%)

PEMF=pulsed electromagnetic field.

significant differences in age, gender, race, litigation status, worker's compensation claims, or smoking status between the two groups.

There were no statistically significant differences between groups with regard to the preoperative diagnosis. The diagnosis of herniated nucleus pulposus was applied to 37 (23.1%) patients in the control group and to 44 (27.0%) patients in the PEMF group. Twenty-nine (18.1%) control patients and 29 (17.8%) study patients had cervical spondylosis. A diagnosis of both herniated nucleus pulposus and spondylosis was given to 94 (58.8%) control patients and to 90 (55.2%) patients receiving PEMF stimulation.

Medical issues reported in patients' histories included diabetes mellitus, cardiovascular disease, lumbar spine disorders (including low back pain), and arthritis (Table 2). There were no appreciable differences in the reported problems between the two groups. There were 42 (26.3%) control patients and 51 (31.3%) patients in the PEMF group without reported medical problems.

#### Procedures and outcomes

Most of the patients had two-level surgeries: 100 (62.5%) control patients and 92 (56.4%) PEMF patients. Thirty-two (20.0%) control patients and 38 (23.3%) PEMF patients underwent single-level surgeries, whereas 26 (16.3%) control patients and 27 (16.6%) PEMF patients had three-level surgeries. Only two (1.3%) patients in the control group and six (3.7%) in the PEMF group underwent four-level procedures. There were no statistically significant differences between the two groups with regard to the number of levels operated on.

#### Patient evaluability at 6 months postoperatively

In the control group, 118 (73.8%) patients were evaluable at 6 months postoperatively. Similarly, 122 (74.9%) patients in the PEMF group were evaluable at that time point. Of the control group (PEMF group results in brackets), 13 (8.1%) [15 (9.4%)] voluntarily withdrew, 1 (0.6%) [7 (4.3%)] had violated study protocol, and 28 (17.5%) [19 (11.7%)] had radiographs that were not evaluable (or were not obtained within 2 weeks of the 6-month

Table 2  
Medical history

	Control (N=160)	PEMF (N=163)
None	42	51
Osteoporosis	1	1
Diabetes	13	14
Cardiovascular disease	5	5
Lumbar spine disorder/LBP	16	21
Previous cervical spine surgery	6	3
Shoulder/hand problems	12	6
Arthritis	5	1
Other	12	9

PEMF=pulsed electromagnetic field; LBP=low back pain.

postoperative window). Films deemed "not evaluable" by the reviewers typically involved fusion at C6–7 or C7–T1 where the shoulders precluded adequate lateral views.

#### Intent-to-treat analysis

Eighty-three patients were nonevaluable at 6 months postoperatively. An intent-to-treat analysis was performed to compare the actual results of the study with those obtained when various assumptions are made regarding the outcomes of patients who did not complete the study (Table 3). If one assumes that all patients with missing 6-month data did not fuse, the worst possible scenario, the PEMF and control groups' fusion rates drop to 65.6% and 56.3%, respectively ( $p=.0835$ ). Alternatively, if all patients with missing data fused, the PEMF fusion rate would increase to 85.9% and that of the control would be 76.3% ( $p=.0269$ ). Finally, if one assumed that the data obtained at the patient's last visit were the final results, the PEMF fusion rate would be 78.2%, and the control fusion rate would be 64.8% ( $p=.0127$ ). The actual fusion rates for the 240 evaluable patients in the PEMF and control groups at the 6-month time point of the study were 83.6% and 68.6% ( $p=.0065$ ), respectively. Thus, these results fall between the fusion rates of the best-case scenario (ie, all missing outcomes were fused) and the rates obtained by analyzing data from the last patient encounter.

#### Fusion rates

At 6 months after surgery, 81/118 (68.6%) patients in the control group had fused, as judged by the study criteria described, and 102/122 (83.6%) patients in the PEMF group had fused ( $p=.0065$ ). For the patients available for follow-up at 12 months, radiographically confirmed fusion was achieved in 104/120 (86.7%) of the control patients and 116/125 (92.8%) of the PEMF patients ( $p=.1129$ ).

The radiographic fusion rates at 6 months for the various studied demographics are presented in Table 4. The table

Table 3  
Intent-to-treat analysis at 6 months

Imputation	Patients	Fused (rate)	p Value
Missing patients fused			
Control	160	122 (76.3%)	.0269
PEMF	163	140 (85.9%)	
Status at last patient visit			
Control	139	90 (64.8%)	.0127
PEMF	142	111 (78.2%)	
Missing patients did not fuse			
Control	160	90 (56.3%)	.0835
PEMF	163	107 (65.6%)	
Actual results			
Control	118	81 (68.6%)	.0065
PEMF	122	102 (83.6%)	

PEMF=pulsed electromagnetic field.



Table 4  
Radiographic fusion rates at 6 months by demographics

	Control (N=118)	PEMF (N=122)	p Value
Gender			
Male	38/59 (64.4%)	55/68 (80.9%)	.0053
Female	43/59 (72.9%)	47/54 (87.0%)	
Age			
<50	61/82 (74.4%)	64/75 (85.3%)	.0040
≥50	20/36 (55.6%)	38/47 (80.9%)	
Smoking status			
Nonsmoking	36/53 (67.9%)	49/61 (80.3%)	.0172
Smoking	45/65 (69.2%)	53/61 (86.9%)	
Levels operated			
Single	21/25 (84.0%)	24/26 (92.3%)	.0062
Multiple	60/93 (64.5%)	78/96 (81.3%)	

PEMF=pulsed electromagnetic field.

illustrates the fact that PEMF stimulation significantly improved the fusion rate at 6 months regardless of gender, age, smoking status, or number of levels operated on. However, the use of PEMF stimulation did not result in a statistically significant difference in fusion rates at 12 months postoperatively.

Table 4 also allows for an analysis of the factors that influenced fusion rates for patients undergoing ACDF with allograft and an anterior cervical plate in this study when PEMF stimulation was not used postoperatively. By examining the control group data, one can determine which demographic factors had the most influence on osseous union (Table 5). At 6 months postoperatively, patients less than 50 years of age in the control group had an overall fusion rate of 74.4%, whereas only 55.6% of control patients 50 years of age or older fused by this time point. This difference was statistically significant ( $p=.0423$ ). At 1 year, 91.6% of patients less than 50 years of age were rated as fused, whereas only 75.7% of patients 50 years of age or older had osseous unions ( $p=.0180$ ). Interestingly, there were no significant differences in fusion rates at 6 months or 1 year between smokers and nonsmokers in the control group. Finally, although there was a strong trend toward lower fusion rates at 6 months for multilevel versus single-level patients in the control group (64.5% vs. 84.0%), this difference did not quite reach statistical significance ( $p=.0623$ ). The large number of two-level fusions (62.5%) in the multilevel control group may account for the lack of significance.

#### Visual analog scale

The mean VAS scores at rest preoperatively were 6.5 and 6.4 cm for the control and PEMF groups, respectively

(Fig. 2, top, left). Most improvement was observed during the first 6 months after surgery. Six months postoperatively, the control group score was 2.3 cm, whereas the PEMF group score was 2.4 cm. At 12 months, the control group score was 2.0 cm, and the PEMF group score was 2.2 cm. The VAS scores during activity (Fig. 2, top, right) demonstrated a similar trend and values when compared with the scores at rest. Preoperatively, the control and stimulation groups had VAS scores during activity of 7.7 and 7.8 cm, respectively. At 6 months after the index procedure, the scores decreased to 3.1 and 3.4 cm, respectively. By 12 months, the control group VAS score was 2.9 cm, and that of the PEMF group was 3.0 cm. There were no statistically significant differences between groups at any time point.

#### Neck disability index

Preoperatively, the mean NDI scores for the control and stimulation groups were 45.6 and 48.0, respectively (Fig. 2, bottom, left). Six months after surgery, the respective scores dropped to 23.0 and 31.0. At 12 months postoperatively, the mean disability index score for the control group fell to 22.8, and that of the PEMF group fell to 25.6. Differences between groups were not statistically significant.

#### Mean SF-12 physical health scores

The mean SF-12 physical health scores for both the control (33.2) and PEMF (33.1) groups were essentially the same preoperatively (Fig. 2, bottom, right). Most improvement for both groups occurred during the first 6 months after surgery. At that time, the control and PEMF groups had scores of 41.9 and 40.8, respectively, and at 12 months postoperatively, the scores were 45.1 and 41.4, respectively. There were no statistically significant differences between the groups.

#### Safety

Comparison of both anticipated (Table 6) and unanticipated adverse events after ACDF did not demonstrate any statistically significant differences between the groups, indicating that the PEMF device is safe for this use.

#### Discussion

The factors affecting fusion rates after ACDF surgery have been extensively studied. Multilevel surgery, smoking, and the use of allograft bone have been reported to be negative risk factors for fusion. However, the vast majority of studies that report on fusion rates after ACDF are

Table 5  
Chi-square analysis of control group fusion rate by demographic variables

	<50 y (%)	≥50 y (%)	p	Nonsmoker (%)	Smoker (%)	p	Single-level (%)	Multilevel (%)	p
Month 6	74.4	55.6	.0423	67.9	69.2	.8791	84.0	64.5	.0623
Month 12	91.6	75.7	.0180	86.8	86.6	.9712	92.9	84.8	.2711

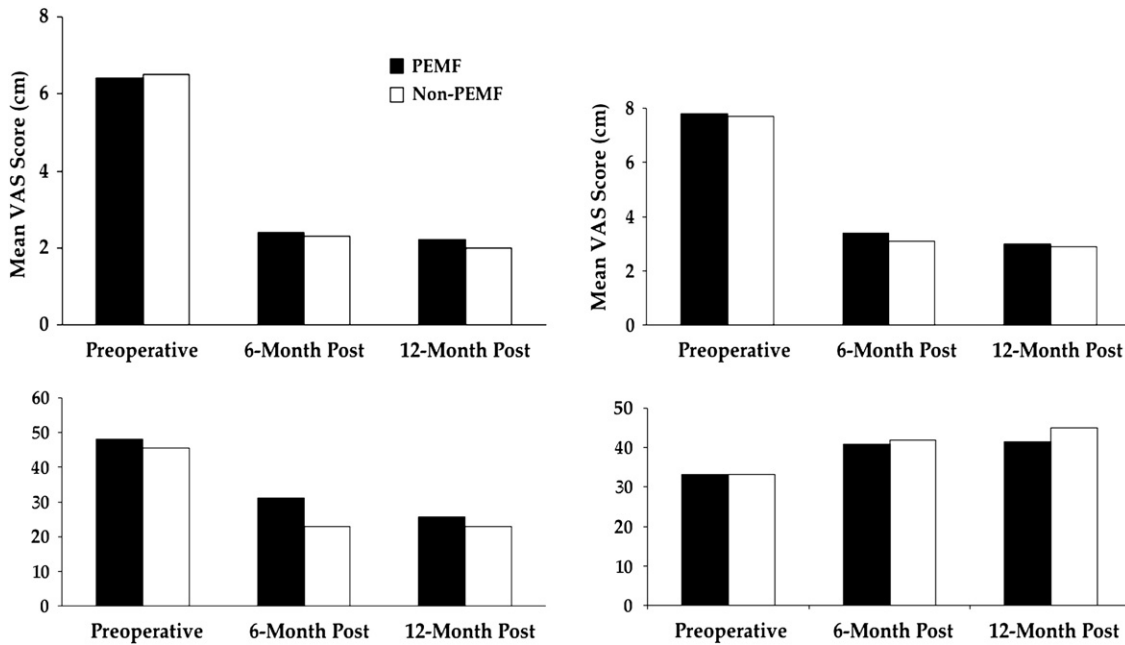


Fig. 2. Mean visual analog scale (VAS) scores (Top, left) at rest and (Top, right) during activity (Bottom, left), mean neck disability index (NDI) scores, and (Bottom, right) SF-12 mean physical health scores for pulsed electromagnetic field (PEMF)-stimulated and control patients recorded preoperatively, at 6 and 12 months postoperatively.

retrospective and uncontrolled, which may account for the large range of reported results. Perhaps adding to this variability is the fact that no single standard currently exists by which fusion rates are assessed. Further, the type of evaluator used (blinded, independent vs. operating surgeon) has been inconsistently reported in the studies, as have been the methods used to define fusion.

Reported fusion rates from retrospective studies for single- and multilevel anterior cervical surgery using allograft bone with instrumentation are 92% to 100% and 72% to 100%, respectively [10–12]. Fusion rates using autograft bone with instrumentation for the same surgery have been reported to be 53% to 100% [7,8,12–16]. Bolesta et al. [7] reported a 53% nonunion rate in a prospective analysis of 15 patients with three- and four-level anterior cervical fusions. Smoking has been shown in several retrospective reviews to be associated with high pseudoarthrosis rates [9,11,17].

Table 6  
Summary of anticipated adverse events—Month 6

	Control (%)	PEMF (%)
Increased neck pain	6.25	9.82
Tenderness	0.63	0.00
Numbness/tingling	3.75	2.45
Headache	1.25	2.45
Dizziness	1.25	0.61
Rash	0.00	0.61
Rapid/irregular pulse	0.00	0.61
Shortness of breath	0.00	0.61
Nausea	0.00	1.23
Ringling in ears	0.00	0.61

PEMF=pulsed electromagnetic field.

Martin et al. studied the effect of smoking in patients after ACDF using allograft bone with instrumentation [11]. The reported fusion rate in nonsmokers for single-level procedures was 92%, compared with 85% in smokers. The difference for two-level procedures was more pronounced; the rate of fusion was 72% and 50% for nonsmokers and smokers, respectively. Cauthen et al. [17] reported an overall fusion rate of 85% in nonsmokers and 77% in smokers after single- or multilevel ACDF using autograft and allograft bone without instrumentation. Additionally, Hilibrand et al. [9] showed a 50% nonunion rate among smokers who underwent multilevel anterior cervical discectomy with interbody fusion using an autograft without fixation, compared with 69% in the control group. Bose [18] and colleagues, however, did not find a significant effect of smoking on fusion rate in their retrospective analysis of 106 patients. They reported a 96.67% and 97.83% fusion rate in smokers and nonsmokers, respectively, after multilevel ACDF with fixation.

This is the only randomized, controlled clinical trial to date reporting on the use of PEMF stimulation to enhance bone healing after anterior cervical discectomy and interbody fusion. By virtue of the study design, it also provides controlled data on fusion rates using allograft bone and instrumentation stratified by gender, age, number of operated levels, and smoking status. The statistically significant results reported herein indicate that PEMF stimulation enhances fusion rates after instrumented ACDF with allograft bone at 6 months (PEMF, 83.6%; control, 68.6%). The overall fusion rates at 12 months for the stimulated and control groups were 92.8% and 86.7%, respectively, which did not reach statistical significance ( $p=.1129$ ).

The results of this study also demonstrate a statistically significant difference in fusion rates at 6 months (74.4% vs. 55.6%,  $p=.0423$ ) and 12 months (91.6% vs. 75.7%,  $p=.0180$ ) postoperatively in patients younger than 50 years compared with older patients. The study did not identify smoking to be a risk factor for pseudoarthrosis among patients undergoing ACDF with allograft and an anterior cervical plate, as rates of fusion for smokers and nonsmokers were nearly identical in the control group. There was a strong trend toward a lower fusion rate for multilevel versus single-level ACDF in this study (64.5% vs. 84.0%), but this did not quite reach statistical significance ( $p=.0623$ ).

The precise biological mechanisms by which PEMF stimulation promotes bone formation remain unclear. Preclinical and clinical efforts have demonstrated that PEMF stimulation is efficacious in healing long bone nonunions [19] and in accelerating bone callous organization [20] and cancellous bone graft incorporation [21–23]. It has also been shown to have positive effects on soft-tissue injuries, including those to ligaments [24], tendons [25], and peripheral nerves [26]. Further, in an osteoporotic, postmenopausal rat model, PEMF stimulation was shown to have osteogenic potential [27].

In this study, PEMF stimulation appeared to accelerate the incorporation of interbody allograft bone into the cervical spine, as measured by fusion rates at 6 months postoperatively (83.6% vs. 68.6%,  $p=.0065$ ). It did not, however, result in a statistically significant difference in the fusion rate at 12 months follow-up. There were also no significant differences in patient-derived outcome measures between the PEMF and control groups at any point in time. Thus, although PEMF stimulation appeared to hasten bone healing in this randomized trial, it did not result in a significant advantage in terms of ultimate fusion rates or clinical outcomes in the overall study population. Interestingly, the patients at greatest risk for nonunion in this study were those 50 years or older. Detailed analysis of the results of PEMF stimulation in this subgroup is ongoing.

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