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Pulsed electromagnetic field stimulation may improve fusion rates in cervical arthrodesis in high-risk populations

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doi: 10.1302/2046-3758.72.BJR-2017-0221.R1

Bone Joint Res 2018;7:124–130.

Objectives

Pulsed electromagnetic field (PEMF) stimulation was evaluated after anterior cervical discectomy and fusion (ACDF) procedures in a randomized, controlled clinical study performed for United States Food and Drug Administration (FDA) approval. PEMF significantly increased fusion rates at six months, but 12-month fusion outcomes for subjects at elevated risk for pseudoarthrosis were not thoroughly reported. The objective of the current study was to evaluate the effect of PEMF treatment on subjects at increased risk for pseudoarthrosis after ACDF procedures.

Methods

Two evaluations were performed that compared fusion rates between PEMF stimulation and a historical control (160 subjects) from the FDA investigational device exemption (IDE) study: a *post hoc* (PH) analysis of high-risk subjects from the FDA study (PH PEMF); and a multicentre, open-label (OL) study consisting of 274 subjects treated with PEMF (OL PEMF). Fisher's exact test and multivariate logistic regression was used to compare fusion rates between PEMF-treated subjects and historical controls.

Results

In separate comparisons of PH PEMF and OL PEMF groups to the historical control group, PEMF treatment significantly ($p < 0.05$, Fisher's exact test) increased the fusion rate at six and 12 months for certain high-risk subjects who had at least one clinical risk factor of being elderly, a nicotine user, osteoporotic, or diabetic; and for those with at least one clinical risk factor and who received at least a two- or three-level arthrodesis.

Conclusion

Adjunctive PEMF treatment can be recommended for patients who are at high risk for pseudoarthrosis.

Cite this article: *Bone Joint Res* 2018;7:124–130.

Keywords: Anterior cervical discectomy and fusion, Pulsed electromagnetic field, Arthrodesis

Article focus

- The focus of this article is to evaluate the effect of pulsed electromagnetic field (PEMF) stimulation treatment on fusion rates for subjects at increased risk for pseudoarthrosis after anterior cervical discectomy and fusion procedures.
- Another purpose of the article is to evaluate the long-term (12-month) effect of PEMF treatment on fusion rates.

Key messages

- After anterior cervical discectomy and fusion (ACDF), adjunctive pulsed electromagnetic field (PEMF) stimulation significantly increased the fusion rate relative to a historical control at six and 12 months for subjects who were at risk for pseudoarthrosis.
- Subjects who responded to PEMF with increased fusion rates included subjects who had at least one risk factor of being elderly, a nicotine user, osteoporotic, or diabetic; or had at least one risk factor and received at least a two- or three-level arthrodesis.
- Two evaluations confirmed these results: a *post hoc* comparative analysis of PEMF-

and control-treated high-risk subjects from a United States Food and Drugs Administration Investigational device exemption study; and a multicentre, retrospective cohort study consisting of 274 subjects treated with PEMF.

Strengths and limitations

- A strength of this study was the availability of data from two large patient data sets.
- A limitation is that the open-label study compared results with a historical control rather than a randomized concurrent control.

Introduction

The safety and effectiveness of pulsed electromagnetic field (PEMF) stimulation as an adjunct for bone healing in procedures including fracture repair and spinal arthrodesis has previously been described.[1-5] However, there has been only one published study on the adjunctive use of PEMF stimulation for cervical arthrodesis that resulted in premarket approval from the United States Food and Drug Administration (FDA).[6] In a randomized, controlled clinical trial of PEMF for anterior cervical discectomy and fusion (ACDF), PEMF significantly improved the fusion rate at six months postoperatively as compared with control subjects who did not receive PEMF treatment.[6] One theoretical mechanism of action for this result is that PEMF stimulates the cellular function of progenitor cells and osteoblasts[7-10] and bone morphogenetic protein expression,[11] which leads to increased bone formation and fusion rates.

A successful spinal arthrodesis may be influenced by numerous clinical risk factors including being elderly, a nicotine user, osteoporotic, or diabetic. These comorbidities have been linked to higher rates of nonunion or delayed union, inhibition of bone repair, and/or higher complication rates.[12-19] A risk factor for surgical complication is multilevel arthrodesis, which is associated with an increased rate of reoperation, higher pseudoarthrosis rates, and longer time to fusion as compared with single-level procedures,[20-22] and is a known risk factor for nonunion after ACDF.[23-24] For subjects with risk factors that compromise bone healing, adjunctive measures are often recommended.[18]

The aforementioned FDA study also described an improved fusion rate at 12 months for PEMF stimulation as compared with the control, although the improvement did not reach significance.[6] However, analysis of subjects at risk for compromised bone healing were restricted to those who were at least 50 years of age or were smokers. The purpose of the current evaluation was to obtain additional spinal fusion outcome data for PEMF treatment in high-risk subjects and to evaluate 12-month outcomes to determine the long-term effects of PEMF. Such evaluation is intended to identify the subject and surgical risk factors that benefit most from PEMF treatment.

Patients and Methods

Study design. A retrospective, multicentre, open-label, cohort clinical trial using PEMF was performed in subjects undergoing cervical arthrodesis according to Good Clinical Practice requirements (denoted OL 2014 study). Institutional Review Boards at each institution approved the study and, because the study was retrospective and the patients had already received treatment, waived the requirement for informed consent.

A total of 274 subjects were enrolled at three institutions and were included in the study if they were at least 18 years of age and elected to undergo ACDF surgery with adjunctive use of a PEMF device designed specifically for the cervical spine (Cervical-Stim; Orthofix Inc., Lewisville, Texas). Each subject was required to have one or more of the following risk factors for pseudoarthrosis to be included into the study: at least 65 years of age, required multilevel arthrodesis (up to five levels), prior failed fusion at any cervical level, habitual use of nicotine at the time of surgery, was diabetic, and/or was osteoporotic. The exclusion criteria were for subjects less than 18 years of age who had received an arthrodesis of more than five levels, and who did not have one or more of the risk factors for pseudoarthrosis as defined above. The number of excluded patients was not recorded. Perioperative steroids were utilized and a typical dose, for example 10 mg Decadron IV, was given at the start of surgery and then for one or two doses after surgery depending on the surgeon's preference. There were no restrictions placed on the diagnosis, interbody implant, graft material, surgical procedure, or postoperative care regimen. Surgeries were performed between February 2007 and February 2014. The PEMF prescription was for three to six months.

Endpoints. Two postoperative visits were performed at six (± two) and 12 (± three) months. The primary endpoint was fusion at six and 12 months as determined by the presence of continuous bridging bone on plain films as assessed by the treating surgeon who was not blinded to the clinical symptomology and outcomes.

PEMF Device. Cervical-Stim (Orthofix, Inc., Lewisville, Texas) is a Class III commercial electromagnetic field device approved by the FDA for osteogenesis stimulation. Specifically, it has been approved as an adjunct for cervical spine fusion surgery in patients at high risk for nonunion. The device consists of a single coil placed posteriorly to the cervical spine covering all cervical levels.[25] The PEMF signal for the Cervical-Stim device is characterized by a fundamental (burst) frequency of 15 Hz, a pulse frequency of 3.85 kHz, and magnetic field amplitude of 1.19 mT.

Statistical analysis. PH PEMF and OL PEMF groups were compared with the controls in separate analyses. Fisher's

Table I. Subject demographics, surgical, and clinical risk factors

Variable	OL PEMF (n = 274)	PH PEMF (n = 163)	Control (n = 160)
Mean age, yrs (SD, range)	54.9 (11.2, 29 to 83)*	46.9 (9.4, 24 to 73)	46.7 (9.2, 26 to 72)
Gender, n (%)			
Male	120 (*43.8*)†	90 (*55.2*)	85 (*53.1*)
Female	154 (*56.2*)	73 (*44.8*)	75 (*46.9*)
Ethnic background (%)			
Caucasian	219 (*79.9*)*	151 (*92.6*)	150 (*93.8*)
African-American	27 (*9.9*)	10 (*6.1*)	7 (*4.4*)
Asian	5 (*1.8*)	0 (*0.0*)	0 (*0.0*)
Hispanic	0 (*0.0*)	2 (*1.2*)	3 (*1.9*)
Unknown	23 (*8.4*)	0 (*0.0*)	0 (*0.0*)
At least one RF4 (⩾ 65 yrs)	132 (*48.2*)*	97 (*59.5*)	98 (*61.3*)
At least one RF4 (⩾ 50 yrs)	217 (*79.2*)	118 (*72.4*)	118 (*73.8*)
At least one RF4 (⩾ 65 yrs) and at least 2 levels	120 (*43.8*)	60 (*36.8*)	66 (*41.3*)
At least one RF4 (⩾ 65 yrs) and at least 3 levels	75 (*27.4*)*	18 (*11.0*)	16 (*10.0*)
At least one RF4 (⩾ 50 yrs) and at least 2 levels	200 (*73.0*)*	81 (*49.7*)	86 (*53.8*)
At least one RF4 (⩾ 50 yrs) and at least 3 levels	123 (*44.9*)*	27 (*16.6*)	21 (*13.1*)

*Significant difference compared with the control group ($p < 0.05$ from *t*-test for age, Fisher's exact test for gender and risk factors, and exact chi-squared test for ethnic background)
†Approaching significant difference compared with the control group ($0.05 \leqslant p \leqslant 0.10$ from Fisher's exact test)
OL, open-label; PEMF, pulsed electromagnetic field; PH, *post hoc*; RF4, risk factors (nicotine user, diabetic, osteoporosis; ⩾ 65 years, or ⩾ 50 years)

exact test was used for comparison of binary baseline variables and fusion status at six and 12 months. Pearson's chi-squared test was used for comparison of multicategorical variables. The retrospective power calculation was based on 80% power, 5% two-sided Type-I error, balanced design, and binary fusion outcome. Reported descriptive statistics include mean ± SD and range for continuous variables, and counts and percentages for categorical variables. Multivariate logistic regression was performed to assess the association between fusion outcome and covariates of age, gender, and number of levels. The significance level for all tests was set at a two-sided p-value of less than 0.05. The *post hoc* analyses were not statistically powered.

Results

Demographics and clinical and surgical risk factors. Two evaluations were performed. In the first evaluation, a *post hoc* analysis of the original FDA study population was performed. The second evaluation was a retrospective, multicentre, open-label, cohort clinical study (designated OL 2014) that was performed on subjects who have one or more risk factors for cervical pseudoarthrosis. The demographics from both studies were compared with the historical control group from the FDA study that was provided by the sponsor of this study, Orthofix (Table I).

There were no significant differences between the PEMF- and control-treated populations in the original FDA study.

Of the 274 subjects in the OL 2014 study, 56.2% were female, 43.8% were male, and the mean age was 54.9 years (SD 11.2, range 29 to 83). The PEMF treatment group was significantly older, more ethnically diverse, contained a lower percentage of subjects with at least one RF4 (at least 65 years of age), contained a higher percentage of those same subjects who also received a three-level arthrodesis, and contained a higher percentage of subjects with at least one RF4 (at least 50 years of age) who also received a two- or three-level arthrodesis compared with the FDA control group. In addition, arthrodesis was performed at C2-C3 and C7-T1 for PEMF treatment, whereas the control group did not receive arthrodesis at these levels. However, only ten C2-C3 and 27 C7-T1 levels were operated on, which represents 7.8% of the total number of levels (37/474).

***Post hoc* fusion analysis of the original FDA study data.** From the original FDA population of 160 control subjects and 163 PEMF-treated subjects, the data were stratified by various clinical or surgical factors that place a subject at a higher risk of pseudoarthrosis (Figure 1). These data were not previously reported.[6] At both six and 12 months, PEMF treatment significantly increased fusion rates for subjects who had at least one risk factor of being elderly (at least 50 or 65 years of age), a nicotine user, osteoporotic, or diabetic (RF4) (Table II).

For subjects who received at least a two-level arthrodesis and who had at least one risk factor of being elderly (at least 50 or 65 years of age), a nicotine user, osteoporotic, and/or diabetic, PEMF treatment significantly increased fusion rates compared with the control at both six and 12 months (Table II). For those who received a three-level arthrodesis, PEMF significantly increased fusion rates at 12 months, although the results should be interpreted with caution due to the small sample size.

Multicentre open-label study (OL 2014). There were 274 subjects enrolled in the study in which all subjects presented with surgical risk factors (received a prior failed fusion or a multilevel arthrodesis) and clinical risk factors (65 years of age or older, a nicotine user, osteoporotic, diabetic). The historical control utilized the 160 subjects who were not treated with PEMF in the FDA study,[6] all of whom had at least one of the same risk factors (Fig. 1).

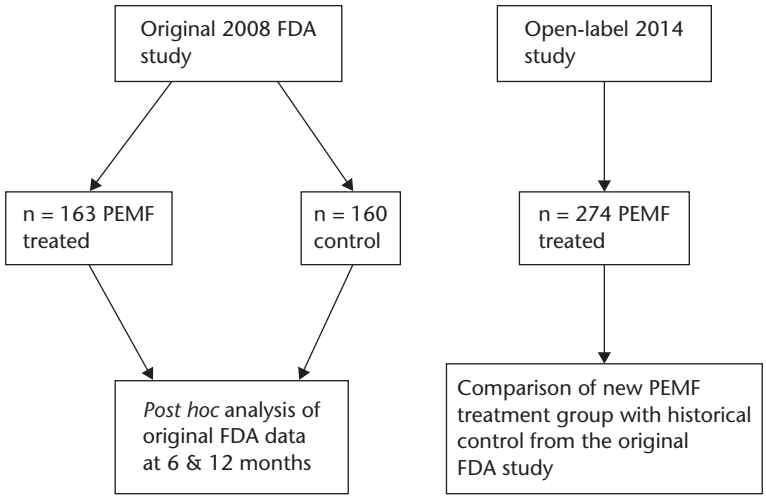

Fig. 1

Schematic of evaluations performed. Two evaluations were performed that compared fusion rates between pulsed electromagnetic field (PEMF) stimulation and a historical United States Food and Drug Administration (FDA) control (160 subjects): a *post hoc* analysis of high-risk subjects from the FDA study, and a multicentre cohort study consisting of 274 subjects treated with PEMF.

Table II. Fusion rates by risk factor (nicotine use, osteoporosis, diabetes, and either age ⩾65 or ⩾50 years)

	6 mths			12 mths		
	OL PEMF	**PH PEMF**	**Control**	**OL PEMF**	**PH PEMF**	**Control**
Clinical risk factors, n (%)						
At least 1 RF4 (⩾65 yrs)	92/118 (*78.0*)†	61/70 (*87.1*)*	50/76 (*65.8*)	125/132 (*94.7*)*	67/69 (*97.1*)*	64/78 (*82.1*)
p-value	0.069	0.0033	N/A	0.0043	0.0033	N/A
At least 1 RF4 (⩾ 50 yrs)	151/200 (*75.5*)*	73/88 (*83.0*)*	57/90 (*63.3*)	201/217 (*92.6*)*	83/88 (*94.3*)*	76/92 (*82.6*)
p-value	0.036	0.0040	N/A	0.013	0.019	N/A
Number of levels, n (%)						
At least 1 RF4 (⩾ 65 yrs) and at least 2 levels	84/108 (*77.8*)*	37/44 (*84.1*)*	29/51 (*56.9*)	114/120 (*95.0*)*	41/41 (*100*)*	38/50 (*76.0*)
p-value	0.0088	0.0068	N/A	0.0006	0.0004	N/A
At least 1 RF4 (⩾65 yrs) and at least 3 levels	55/68 (*80.9*)*	7/12 (*58.3*)	3/10 (*30.0*)	73/75 (*97.3*)*	11/11 (*100*)*	5/11 (*45.5*)
p-value	0.0021	0.23	N/A	< 0.0001	0.012	N/A
At least 1 RF4 (⩾50 yrs) and at least 2 levels	141/185 (*76.2*)*	49/62 (*79.0*)*	36/65 (*55.4*)	186/200 (*93.0*)*	57/60 (*95.0*)*	50/64 (*78.1*)
p-value	0.0024	0.0051	N/A	0.0018	0.0081	N/A
At least 1 RF4 (⩾50 yrs) and at least 3 levels	87/114 (*76.3*)*	9/19 (*47.4*)	3/14 (*21.4*)	117/123 (*95.1*)*	17/19 (*89.5*)*	6/13 (*46.2*)
p-value	< 0.0001	0.16	N/A	< 0.0001	0.015	N/A

*Significant difference compared with the control group ($p < 0.05$ from Fisher's exact test)
†Approaching significant difference compared with the control group ($0.05 \leqslant p \leqslant 0.10$ from Fisher's exact test)
OL, open-label; PEMF, pulsed electromagnetic field; PH, *post hoc*; RF4, risk factors (nicotine user, osteoporosis, diabetes, age ⩾65 years or ⩾50 years); N/A, not applicable

Fusion outcomes. To directly compare the findings of the OL 2014 study with the *post hoc* evaluation, the OL 2014 study was stratified into the same clinical and surgical risk factors, and the fusion rate for each PEMF-treated subgroup was compared with the corresponding control at both six and 12 months (Table II). At six months, PEMF treatment significantly increased fusion rates for two groups: those subjects who had at least one risk factor of being elderly (at least 50 or 65 years of age), nicotine users, osteoporotic, and/or diabetic; and those who had at least one risk factor and received at least a two- or three-level arthrodesis (Table II). Significantly increased fusion rates following PEMF treatment were observed at both six and 12 months in these groups (Table II).

Stratification by demographic groups revealed no significant differences in fusion rate between PEMF and the control group for gender, ethnic background, or subjects on disability benefit due to the neck condition reported in this study, or for those who received worker's compensation.

To assess the association between fusion outcome and age, gender, and number of levels, a multivariate logistic regression was performed based on OL PEMF and FDA control groups. The association of fusion incidence with PEMF treatment was strong and significant for subjects who had at least one of four risk factors at both six and 12 months (odds ratio ranged from 2.7 to 5.6) (Table III). For subjects with these risk factors, there was no association

Table III. Results from multivariate logistic regression analyses using open-label pulsed electromagnetic field stimulation (OL PEMF) and United States Food and Drug Administration (FDA) control subjects with at least one RF4 (⩾65 years or ⩾50 years)

Covariates	Odds ratio (outcome fusion)	95% CI	p-value
At least 1 RF4 (⩾65 yrs)			
Fusion at 6 mths (142/194)			
Treatment (OL PEMF *vs* control)	3.370	1.475 to 8.068	0.0048*
Age	0.963	0.930 to 0.995	0.029*
Gender (female *vs* male)	1.052	0.535 to 2.059	0.88
Number of levels	0.900	0.587 to 1.374	0.63
Fusion at 12 mths (189/210)			
Treatment (OL PEMF *vs* control)	5.611	1.783 to 19.409	0.0043*
Age	0.982	0.934 to 1.029	0.45
Gender (female *vs* male)	1.333	0.519 to 3.453	0.55
Number of levels	0.857	0.453 to 1.621	0.63
At least 1 RF4 (⩾50 yrs)			
Fusion at 6 mths (208/290)			
Treatment (OL PEMF *vs* control)	2.759	1.429 to 5.416	0.0027*
Age	0.966	0.936 to 0.994	0.021*
Gender (female *vs* male)	1.037	0.610 to 1.760	0.89
Number of levels	0.943	0.675 to 1.316	0.73
Fusion at 12 mths (277/309)			
Treatment (OL PEMF *vs* control)	3.005	1.231 to 7.435	0.016*
Age	0.988	0.947 to 1.029	0.56
Gender (female *vs* male)	1.332	0.630 to 2.839	0.45
Number of levels	0.980	0.599 to 1.609	0.94

*Significant difference compared with the control group ($p < 0.05$, Wald chi-squared test)
CI, confidence interval; RF4, risk factors (nicotine user, osteoporosis, diabetes, age ⩾65 years or ⩾50 years)

between fusion rates and either gender or two- or three-level arthrodesis (Table III).

Discussion

In a prospective, multicentre, randomized, and controlled FDA clinical study for anterior cervical discectomy and fusion (ACDF), PEMF treatment significantly increased the fusion rate as compared with the control that lacked PEMF stimulation at six months.[6] Furthermore, within some demographic and surgical subpopulations, namely for subjects who were 50 years of age or older or that received multilevel arthrodesis, PEMF also significantly increased the fusion rate at six months, although the publication did not report the fusion rate at 12 months or for other clinical populations at risk of pseudoarthrosis.

Clinical factors such as advanced age, nicotine use, osteoporosis, and diabetes, as well as surgical factors such as multilevel arthrodeses, have been postulated to potentially negatively impact bone healing. As these factors are associated with lower fusion rates, a *post hoc* analysis was performed on high-risk subgroups from the FDA study in order to elucidate the effect of PEMF on these high-risk populations. The *post hoc* analysis demonstrated that PEMF significantly increased fusion rates for subjects with clinical risk factors of being at least 50 or 65 years of age, a nicotine user, osteoporotic, and/or diabetic. In addition, when these subjects also received at least a two-level arthrodesis, PEMF treatment significantly increased fusion rates. Significantly increased fusion rates after PEMF stimulation in these stratified populations was observed at both six and 12 months.

To obtain additional high-risk subjects who represented everyday clinical practice, a multicentre open-label study (referred to as OL 2014) evaluated the effect of PEMF stimulation on fusion rates and this was compared with the historical control group. Both the *post hoc* and the OL 2014 studies identified risk groups that consistently and significantly increased fusion rates after PEMF treatment as compared with the control group at 12 months. These were subjects who had at least one risk factor of being elderly (at least 50 or 65 years of age), nicotine users, osteoporotic, or diabetic, or who had at least one risk factor and received at least a two- or a three-level arthrodesis. In addition, there was a strong association for PEMF treatment leading to increased fusion rates for those subjects who had at least one of the four risk factors at both six and 12 months.

This is the first report to show that PEMF treatment significantly increased fusion rates at 12 months for several high-risk populations that received ACDF. Thus, this evaluation further delineates the risk factors for subjects who may benefit from adjunctive PEMF treatment and demonstrates that the significant PEMF-mediated increase in fusion rates extends up to 12 months, even though the maximum duration of the PEMF prescription was only six months.

Overall, PEMF treatment increased the fusion rate in subjects who have compromised biologic activities (such as the elderly, nicotine users, and diabetics). Osteoblast and/or stem cell functions are impaired in subjects with diabetes mellitus[26-29] and in elderly subjects,[30-31] and nicotine has been shown to decrease the proliferation rates

of osteoblasts.[32] At the cellular and molecular level, PEMF has been demonstrated to: promote earlier osteogenic differentiation of bone marrow stromal cells;[9] increase bone morphogenetic protein expression;[11] increase osteoprogenitor or bone marrow derived mesenchymal stem cell (MSC) deposition of early, late, and terminal osteogenic markers;[8,10,11] and increase proliferation of human osteoblasts.[7] Thus, a hypothetical mechanism of action for the PEMF effect on increased fusion rates is stimulation of the cellular function of MSC and osteoblasts, which, in turn, overcomes biological deficiencies in these high-risk groups.

Limitations to the OL 2014 study include the use of a historical control. The control is valid since it was part of a prospective, randomized study that was used for FDA approval of the PEMF device, and used the same timepoints and fusion assessment (plain films) as were used in the OL 2014 study. Although prospective controls are preferred and are a requirement of Level I studies, historical controls provide a valuable reference and a more robust level of evidence (Level III) as compared with noncontrolled studies (Level IV).[33] Since the OL 2014 study and the historical control group utilized an anterior approach and fixation with plate and screws, the approach and rigid fixation were not potential variables for fusion rates. However, since the surgeons were not restricted with the subject diagnosis, their use of interbody spacer or graft material, these factors may have affected outcomes, and the impact of these on the outcome was not evaluated. To better understand the potential effect of the interbody spacer on fusion rates, four publications were identified, and no significant differences in the fusion rates between structural allograft or polyetheretherketone (PEEK) cages and tricortical autograft spacers were reported.[34-37] Furthermore, there were no differences in fusion rates reported between subjects treated with PEEK or titanium cages.[38]

The results of this OL 2014 clinical study confirm previous reports that PEMF stimulation is an effective adjunct to achieve fusion in a typical subject population, including those with comorbidities. Specifically, adjunctive PEMF treatment significantly increased fusion rates after ACDF relative to historical controls who had at least one risk factor of being elderly, a nicotine user, osteoporotic, and/or diabetic. Additionally, when the subjects with these risk factors received at least a two- or three-level arthrodesis, PEMF treatment resulted in significantly increased fusion rates at 12 months. Thus, PEMF treatment is recommended as an adjunct for ACDF for these patients. However, appropriately powered studies are required to confirm these findings and assess the effect of PEMF on other patient populations. PEMF treatment may be a valuable adjunct for augmenting cervical spinal fusion rate in some cases with high-risk subjects.

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Funding Statement

- The study was supported by a grant from Orthofix, who also supported the collection, analysis, and interpretation of data, and the preparation of the manuscript.

Author Contributions

- D. Coric: Performing surgery.
- D. E. Bullard: Performing surgery.
- V. V. Patel: Performing surgery.
- J. T. Ryaby: Designing the study, Analyzing the data, Reviewing the manuscript.
- B. L. Atkinson: Analyzing the data, Writing the manuscript.
- D. He: Compiling the data, Statistical analysis.
- R. D. Guyer: Analyzing the data, Reviewing the manuscript.

Conflict of Interest Statement

- RDG, DEB, DC, and WP report consultancy fees and/or grants for participation. JTR reports employment, patents, and stock. DH and BLA report consultancy fees, travel support, and/or review activity support. Support was provided by Orthofix.