Spine

Volume 27(13) 1 July 2002 pp 1383-1388

Combined Magnetic Fields Accelerate and Increase Spine Fusion: A Double-Blind, Randomized, Placebo Controlled Study

[Randomized Trial]

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Acknowledgment date: July 21, 2000.
First revision date: February 21, 2001.
Second revision date: May 30, 2001.
Acceptance date: January 7, 2002.
Device Status/Drug Statement: The device(s)/drug(s) is/are FDA-approved or approved by corresponding national agency for this indication.
Conflict of Interest: Corporate/industry funds were received to support this work. One or more of the author(s) has/have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this manuscript:*e.g.*, honoraria, gifts, consultancies, royalties, stocks, stock options, decision-making position.

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Outline

Graphics

Abstract^

Study Design. The clinical study conducted was a prospective, randomized, double-blind, placebo-controlled trial.

Objectives. The purpose of this study was to evaluate the effect of combined magnetic fields on the healing of primary noninstrumented posterolateral lumbar spine fusion.

Summary of Background Data. Combined magnetic fields, a new type of biophysical stimulus, have been shown to act by stimulating endogenous production of growth factors that regulate the healing process. This is the first placebo-controlled study to assess the effect of an electromagnetic stimulus on primary noninstrumented posterolateral lumbar spine fusion surgery as well as the first evaluation of combined magnetic fields as an adjunctive stimulus to lumbar

spine fusion.

Methods. This multicenter investigational study was conducted at 10 clinical sites under an Investigational Device Exemption from the United States Food and Drug Administration. Eligible patients had one-level or two-level fusions (between L3 and S1) without instrumentation, either with autograft alone or in combination with allograft. The combined magnetic field device used a single posterior coil, centered over the fusion site, with one 30-minute treatment per day for 9 months. Randomization was stratified by site and number of levels fused. Evaluation was performed 3, 6, and 9 months after surgery and 3 months after the end of treatment. The primary endpoint was assessment of fusion at 9 months, based on radiographic evaluation by a blinded panel consisting of the treating physician, a musculoskeletal radiologist, and a spine surgeon.

Results. Of 243 enrolled patients, 201 were available forevaluation. Among all patients with active devices, 64% healed at 9 months compared with 43% of patients with placebo devices: a significant difference ($P = 0.003$ by Fisher's exact test). Stratification by gender showed fusion in 67% of women with active devices, compared with 35% of those with placebo devices ($P = 0.001$ by Fisher's exact test). By contrast, there was not a statistically significant effect of the active device in this male study population. In the overall population of 201 patients, repeated measures analyses of fusion outcomes (by generalized estimating equations) showed a main effect of treatment, favoring the active treatment ($P = 0.030$). In a model with main effect and a time by treatment interaction, the latter was significant ($P = 0.024$), indicating acceleration of healing. Performed in the full sample of 243 patients, results of the intent-to-treat analysis were qualitatively the same as in the evaluable sample of 201 patients.

Discussion. This investigational study demonstrates that combined magnetic field treatment of 30 min/d increases the probability of successful spine fusion, and statistical analysis using the generalized estimating equations model suggests an acceleration of the healing process. This is the first randomized clinical trial of noninstrumented primary posterolateral lumbar spine fusion, with evaluation by a blinded, unbiased panel. This is the first double-blind study performed to date assessing noninstrumented fusion outcome with extremely critical radiographic criteria. The lower overall fusion rates in this study are attributed to the high-risk patient group with an average age of 57 years, the use of noninstrumented technique with posterolateral fusion only, and the reliance on extremely critical radiographic and clinical criteria and blinded panel for fusion assessment without surgical confirmation.

Conclusions. In conclusion, the adjunctive use of the combined magnetic field device was statistically beneficial in the overall patient population, as has been shown in previous studies of adjunctive bone growth stimulation for spine fusion. For the first time, stratification of fusion success data by gender demonstrated that the female study population responded positively to the adjunctive combined magnetic field treatment, with no statistically significant effect observed in the male study population. Adjunctive use of the combined magnetic field device significantly increased the 9-month success of radiographic spinal fusion and showed an acceleration of the healing process.

Electrical and electromagnetic fields have been shown to promote the healing of delayed union and nonunion of bone. Their use as noninvasive therapeutic devices began with their first approval by the U.S. Food and Drug Administration (FDA) in 1979. The concepts underlying electrical and electromagnetic stimulation have fostered the development of several FDA-approved noninvasive bone growth stimulation devices for the treatment of fracture nonunion [2,20,21] (also J.D. Zoltan and J.T. Ryaby, unpublished data), and additional clinical work has been performed on avascular necrosis. [1,3,22] The use of these devices for adjunctive stimulation of spinal fusion began in the 1970s.

Initially, this technology, as applied to clinical spine fusion, was with surgically implantable direct current stimulation devices, as reported by Dwyer et al. [7] in 1974 and later by the randomized trial of Kane. [13] However, although the Kane study was randomized, neither of these studies had a placebo control.

The first use of a noninvasive electromagnetic technology was the study by Mooney, who reported on a double-blind placebo-controlled trial of pulsed electromagnetic fields for stimulation of interbody fusions. [16] However, the study was not controlled for use of instrumentation, daily treatment time, or type of graft.

The present study evaluates combined magnetic fields for the noninvasive adjunctive treatment of primary noninstrumented spine fusion. Combined magnetic fields, a new type of biophysical stimulus, are effective with only 30 min/d of stimulation. The use of combined magnetic fields is based on theoretic calculations that predicted coupling to calcium-dependent cellular signaling processes in tissues. [8,15] Combined magnetic fields have been shown to stimulate bone formation and fracture healing in animal model systems. [6,17] They are believed to act by stimulating endogenous production of growth factors that regulate the healing process. [9,10] The first clinical application of combined magnetic fields was on long bone nonunion healing and received FDA approval in 1994. This is the first placebo-controlled study to assess the effect of any electromagnetic stimulus on primary noninstrumented posterolateral lumbar spine fusion surgery as well as the first evaluation of combined magnetic fields as an adjunctive stimulus to lumbar spine fusion.

Methods^

The clinical study was a prospective, randomized, double-blind, placebo-controlled trial [14] conducted under an Investigational Device Exemption (IDE) from the US Food and Drug Administration. The purpose of this clinical study was to investigate the effect of combined magnetic fields as an adjunct to spinal fusion. All patients signed an informed consent and were informed that they would be randomized to receive either active or placebo devices. The investigational sites in this study all received institutional review board approval before initiation of this study. Randomization was accomplished by a computer-generated randomization code provided by an independent third party. A six-block randomization code was used to eliminate bias between investigational sites based on enrollment rates.

Specific inclusion/exclusion criteria are provided in Table 1. The inclusion criteria included patients over 18 years of age, with primary intertransverse fusion without internal fixation of one or two vertebral levels between L3 and S1 within the past 30 days, with autograft alone or in combination with allograft. The major exclusion criterion was no use of internal fixation. Additional exclusion criteria were skeletal immaturity (age <=18 years), pregnancy, vertebral trauma or scoliosis, diagnosis of metastatic cancer, metabolic bone disease, spondylitis, Paget’s disease, moderate to severe osteoporosis, renal dysfunction, uncontrolled diabetes mellitus, or having an implanted cardiac pacemaker. Patients were prescribed with a lumbosacral orthotic and instructed to use it for a minimum

of 2 months after surgery.

Table 1. Study Inclusion/Exclusion Criteria

The patients were enrolled and randomized within 30 days of their fusion surgery. Active and placebo combined magnetic field devices were identical in appearance. The combined magnetic field stimulation was delivered by a portable, microprocessor-controlled, noninvasive device (SpinaLogic, OrthoLogic, Tempe, AZ) that was placed over the spine fusion site. The device is a single coil worn posteriorly (Figure 1) that produces low-energy combined magnetic fields with an integral timer programmed to turn the device off after 30 minutes of treatment. The patient was prevented from using the device for more than one 30-minute treatment in a 24-hour period by microprocessor control. Patient compliance was assessed by a built-in compliance monitor showing the number of completed treatments for the previous 30 days of use as well as the total number of completed treatments since initial application of the device. Placebo devices were programmed to not generate the combined magnetic fields and were identical in appearance to the functioning active devices.

Figure 1. The combined magnetic field device (SpinaLogic) uses a single posterior coil centered over the fusion site.

Clinical and radiographic follow-up evaluations were performed 3, 6, and 9 months after surgery. Routine imaging of the fusion site included anteroposterior, lateral, and oblique radiographs. Computed tomography was performed at 9 months, and lateral flexion-extension radiographs were taken when clinically indicated by the investigator.

The endpoint for the determination of effectiveness was fusion status after 9 months of treatment. The evaluation of fusion outcome was performed by a blinded radiographic review panel composed of the investigator (treating orthopedic spine surgeon) and two reviewers blinded to the device status: a musculoskeletal radiologist and an orthopedic spine surgeon. All treating physicians, reviewers, patients, and the sponsor were blinded as to the activity status of all devices. Safety was determined by evaluating all reports of device-related complications and adverse events.

Fusion status was graded into one of four categories, from no fusion (0) to solid fusion (3) (Table 2). When two levels were involved, the lowest grade at either level was used for the fusion assessment. As defined in the protocol, the grades 0 and 1 were combined into a single category: no fusion (failure). Grades 2 and 3 constituted fusion (success). If the investigator and the radiologist disagreed, the independent spine surgeon reviewer’s rating was used to define fusion status. For this investigation, the treating surgeon had access to all radiographic imaging, clinical, and surgical information. Consistently

with clinical practice, the radiologist was provided the radiographic data alone, and the independent spine surgeon was provided radiographic data as well as pertinent patient information, including demographic, clinical, and operative information.

Table 2. Criteria for Radiographic Assessment of Fusion

Effectiveness was defined by a statistically significant difference between fusion status outcomes in the active and placebo groups. Effectiveness by gender was also performed. Statistical analysis was performed using Fisher's exact test and the Generalized Estimating Equations (GEE) method of Zeger and Liang. [24] The latter analysis makes full use of data at 3 and 9 months, thereby assessing time trends in healing rate.

To examine the sensitivity of our findings to missing or excluded values, series of tabular analyses were run to examine 9-month outcomes in an intent-to-treat analysis. When outcomes were missing, in separate analyses, fusion status was imputed as fused or not fused, or assigned its most recent known value (LVCF). Using each of the three imputation schemes, tabulations were done separately for all subjects, men and women.

Results^

From February 1993 through database closure in July 1998, 243 patients were enrolled in the study at 10 investigational sites (Figure 2). Patient demographics are provided in Table 3 for active and placebo device patients. Of the 243 patients, 201 patients completed the study (83%). Of the 42 nonevaluable patients, 16 patients (8 active, 8 placebo) voluntarily withdrew from the study before the 9-month visit. Ten patients (5 active, 5 placebo) were withdrawn by their physician(s) from the study before the 9-month follow-up. Two patients (one active, one placebo) died during their course of treatment. Both deaths were caused by natural causes, and in neither case was the death considered by the investigator to be related to the application of the SpinaLogic device. An additional 2 patients (placebo) violated the inclusion/exclusion criteria, and the remaining 12 patients missed their follow-up visits or had out-of-window follow-up visits. No patients were withdrawn because of device-related problems. Intent-to-treat analysis considered the withdrawn patients to represent failure. The statistical test results demonstrated that the randomized assignments of patients to the two treatment arms resulted in a well-balanced distribution of patient diagnosis between placebo and active devices (Table 4). No statistically significant differences were found for the clinical variables cited. The average time after surgery for treatment initiation was 19 days.

Figure 2. Study design diagram.

Table 3. Patient Demographics by Randomization Group*One patient did not have demographic information.

Table 4. Patient Diagnosis by Randomization Group and Gender

The data in Table 5 demonstrate a positive effect of the active device in the overall and female patient population. The data show that the treatment did not have a statistically significant effect in the male population. Fusion percentages in the overall patient population increased over the 9-month treatment period in both active and placebo groups (Figure 3). For the 201-patient evaluable population, repeated-measures analysis of fusion outcomes by GEE (Figure 4) demonstrated a main effect of treatment, favoring the active treatment ($P = 0.030$) and, in a separate model, a significant time by treatment interaction ($P = 0.024$), indicating acceleration of healing. Both this analysis and that of the overall patient population (sample size 243, with qualitatively similar results) revealed good agreement between the data and the GEE model. For both active and placebo patients, the proportion of healed patients increased linearly over time, but the V-shaped plot showed that healing was more rapid among active treated patients. For the female population (Figure 5), there was a strongly statistically significant difference between the active and placebo groups at the 6-month, 9-month (study endpoint), and 12-month (3 months after treatment) time points. The 12-month data show that the increase in fusion percentage was maintained beyond the treatment endpoint. The fusion results for the male population showed no statistically significant difference between the active and placebo groups at any time point (Figure 6). The results shown in Table 6 stratify the data by number of levels fused. One-level fusions were significantly improved in the active device group, with an increase of 24% over placebo. Two-level fusions were improved by 18%; however, this difference did not reach statistical significance. The data in Table 7 show the results in the smoking patient population. Only 28 patients were current smokers, and the difference between active and placebo devices did not reach statistical significance.

Table 5. Percent Fusion Success as Determined by the Panel at 9 months

Figure 3. Effect of combined magnetic field treatment compared with placebo on fusion success at each follow-up time point in all patients (n = 201). The treatment endpoint was 9 months.

Figure 4. Observed and predicted fusion proportions, from baseline to 9 months, for all 201 patients. The predicted line is based on a generalized estimating equations model with a time by treatment

interaction term.

Figure 5. Effect of combined magnetic field treatment compared with placebo on fusion success at each follow-up time point in female patients (n = 120).

Figure 6. Effect of combined magnetic field treatment compared with placebo on fusion success at each follow-up time point in male patients (n = 81).

Table 6. Effect of Levels Fused on Fusion Outcome

Table 7. Percent Fusion Success in Current SmokersNA = not available.

The results of the intent-to-treat analysis show a statistically significant treatment effect in favor of the active device for all patients:*P* values were 0.006, 0.015, and 0.007 for imputation as fused, not fused, and LVCF, respectively. For women, there was a statistically significant treatment effect in favor of the active device:*P* values were 0.004, 0.0005, and 0.0003 for imputation as fused, not fused, and LVCF, respectively. For men, there was no statistically significant treatment effects:*P* values were 0.521, 0.684, and 0.838 for imputation as fused, not fused, and LVCF, respectively.

Discussion^

This prospective, double-blind, placebo-controlled study demonstrates that combined magnetic field treatment of 30 min/d increases the probability of achieving a successful one-level or two-level posterolateral spine fusion. In addition, statistical analysis using the GEE model shows an acceleration of the healing process (Figure 4). Intent-to-treat analysis, which considers patient dropouts to be failures, still resulted in a statistically significant benefit of the active device compared to placebo.

There have been no previous studies of adjunctive bone growth stimulation in noninstrumented posterolaterally fused patients. Noninstrumented posterolateral fusions are more difficult to achieve than instrumented fusions and therefore provide a more rigorous test of the efficacy of adjunctive stimulation. In addition, the mean age in this patient population (57 years) provided an additional challenge to successful outcome. Additional information on other technologies for adjunctive stimulation of spine fusion can be found in recent review articles. 5,17,19

This noninvasive technology is unique in requiring only 30 minutes of treatment per day. Previous studies using the other noninvasive technologies required much longer daily treatment times. The study

of Mooney 16 evaluating pulsed electromagnetic fields required a minimum of 4 hours per day of treatment to be included in the compliant users group. In patients who used the pulsed electromagnetic fields device less than 4 hours per day, there was no statistically significant difference between active and placebo device recipients. In the study by Goodwin et al 11 of capacitively coupled field stimulation, patients were required to use the device 24 hours per day. However, patients used the device for an average of only 15–16 hours per day, and 2.6% of patients withdrew because of adverse effects from skin irritation with the electrodes. The relatively low dropout rate of 17% in the study reported here, compared with the 20% dropout rate of Mooney 16 and the unspecified dropout rate of the Goodwin study 11 as noted by Kahanovitz, 12 is likely related to a daily use time of only 30 minutes. This is the first double-blind study performed to date assessing noninstrumented fusion outcome with extremely critical radiographic criteria. Some other studies, however, have shown similar fusion rates in noninstrumented patients. In the study by Dwyer et al, 7 fusion occurred in the noninstrumented control group at a rate of 53.6%. Similarly, Brodsky 4 reported a success rate of 68.5% with no instrumentation, corresponding to the success rate of 65% reported by Zdeblick 23 in a randomized study. The lower overall fusion rates in this study compared with many other reports may have been caused by the high average age of 57 years, the use of noninstrumented technique with posterolateral fusion only, and reliance on extremely critical radiographic and clinical criteria using a blinded panel for fusion assessment. Surgical confirmation was not performed, which may have altered the absolute results. However, this most likely would have similar effects on both populations.

The overall patient population data presented here are analogous to data presented in previous studies of bone growth stimulation for adjunctive spine fusion. 7,11,13,16 In addition, for the first time in the literature, data stratified by gender are presented, demonstrating an increase in the fusion success rate from 35% to 67% in women with the device. No statistically significant effect of the device was noted in the male patient population in this study. The number of patients in this study did not allow stratification by diagnosis at patient entry. Neither this study nor the surgical literature provides any explanation for this finding. These findings should be considered in designing clinical protocols for future studies in spine fusion.

In conclusion, the adjunctive use of the combined magnetic field device for posterolateral fusions was shown to be beneficial in this study. The beneficial results were strongest in the female population included in the study, whereas the male population showed no statistical significance. Adjunctive use of the combined magnetic field device significantly increases the 9-month success rate of radiographic spinal fusion and accelerates the healing process.

Key Points^

* First evaluation of combined magnetic fields for spine fusion.
* First double-blind, placebo-controlled evaluation of an adjunctive stimulation device on noninstrumented fusion.
* Higher mean age of the patients in this study than in other published fusion studies.
* Use of a blinded panel, providing for rigorous assessment of fusion.

Acknowledgments^

The authors acknowledge the participation of the following clinical investigators: Warren R. E. Bourgeois, III, MD, Steven Mather, MD, Brian McCarthy, MD, David McCord, MD, and John Small, MD; and the efforts of Angelika Mozie, and Deborah Koeneman, MS.

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[Key words: combined magnetic fields; electromagnetic stimulation; posterolateral lumbar fusion; placebo-controlled trial; randomized trial]**Spine 2002;27:1383–1389**

Accession Number: 00007632-200207010-00002
