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A Double-Blind Study of Capacitively Coupled Electrical Stimulation as an Adjunct to Lumbar Spinal Fusions

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Study Design. A randomized double-blind prospective comparison with a placebo control. This report of the results is the first in an ongoing study.

Objectives. To evaluate the effect of noninvasive capacitively coupled electrical stimulation on the success rate of lumbar spine fusion surgery, and to compare active with placebo stimulators as adjuncts to contemporary fusion techniques.

Summary of Background Data. Previous studies have established the effectiveness of direct current and electromagnetic field stimulation as adjuncts for some forms of spinal fusion. None of the previous placebo-controlled studies on external bone stimulation included posterolateral fusion techniques, and most were conducted with prior generations of internal fixation hardware.

Methods. The investigation was conducted by 28 U.S. surgeons. Patients with a primary diagnosis of degenerative disc disease with or without other degenerative changes were selected. The study protocol defined success as a clinical outcome rated as excellent or good and a fusion documented as solid by both the investigator and the blinded independent radiologist. Disagreements on radiographic success were resolved by a second blinded independent reviewer.

Results. For the 179 patients who completed treatment and evaluation, the overall protocol success rate (both clinical and radiographic results rated as successes) was 84.7% for the active patients and 64.9% for the placebo patients. This difference is highly significant according to the Yates corrected chi-square test ($P = 0.0043$). Best improvements in patient outcomes (20% or greater success rate) occurred when active stimulation was used in conjunction with posterolateral fusion ($P = 0.006$) and when internal fixation also was incorporated ($P = 0.013$).

Discussion. This study was consistent in that active stimulation improved results for each stratification, although some strata had insufficient numbers of patients for the results to have statistical significance. Improved success rates when capacitively coupled stimulation is added to internal fixation are hypothesized to result from overcoming the biochemical effects of stress shielding.

Conclusions. Capacitively coupled stimulation is an effective adjunct to primary spine fusion, especially for patients with posterolateral fusion and those with internal fixation. [Key words: electrical stimulation, lumbar fusion, pedicle screws, posterolateral lumbar fusion, randomized trial] **Spine 1999;24:1349–1357**

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The concept of electrical stimulation as an adjunct to spinal fusion is a natural extension of the work on healing recalcitrant fractures initiated in the 1970s. Several techniques of delivering therapeutic currents have emerged, and two have been used for spinal fusions and fracture healing. Dwyer[17] published the first report in 1974 on the use of a direct current (DC) implant. By the late 1980s, Kane[25] and Mooney[33] had published reports of randomized placebo-controlled trials, demonstrating efficacy for both DC and external pulsed electromagnetic field (PEMF) systems.

A third type of technology, capacitively coupled electrical stimulation, has been used for nonunion fractures since 1986.[9] The device (SpinalPak system from Biolectron, Inc., Hackensack, NJ) consists of a small microprocessor-controlled stimulator weighing approximately 100 grams (4 ounces) that delivers current via flexible cables to hydrogel surface electrodes. The stimulator delivers a sinusoidal waveform at a frequency of 60 kHz.

The electrical signal used in this study was derived through various *in vitro*,[8] *in vivo*,[3–5,10,11] and mathematical modeling studies.[13,14] Briefly, a dose-response study performed on the management of osteoporosis in the rat vertebra with various capacitively coupled electrical signals pulsed at 60 kHz showed that maximum reversal of lumbar bone mass loss occurred when a calculated current density of 5 μA root mean square/cm^2 and a field of 12 mV root mean square/cm were induced in the vertebral body. The field distributions in the spine and surrounding soft tissues next were determined mathematically, initially for the rat,[14] and then for the human.[13] These studies enabled Brighton's[13] group to determine the number and location of surface (skin) electrodes and the magnitude of the output signal required to produce the same current density (5 μA root mean square/cm^2) and the same field (12 mV root mean square/cm) in the human vertebra as that shown to be effective in restoring bone mass in the rat vertebra.

In the human model, an output signal of 5 V peak to peak and a 7.1- to 10.5-mA current (root mean square)

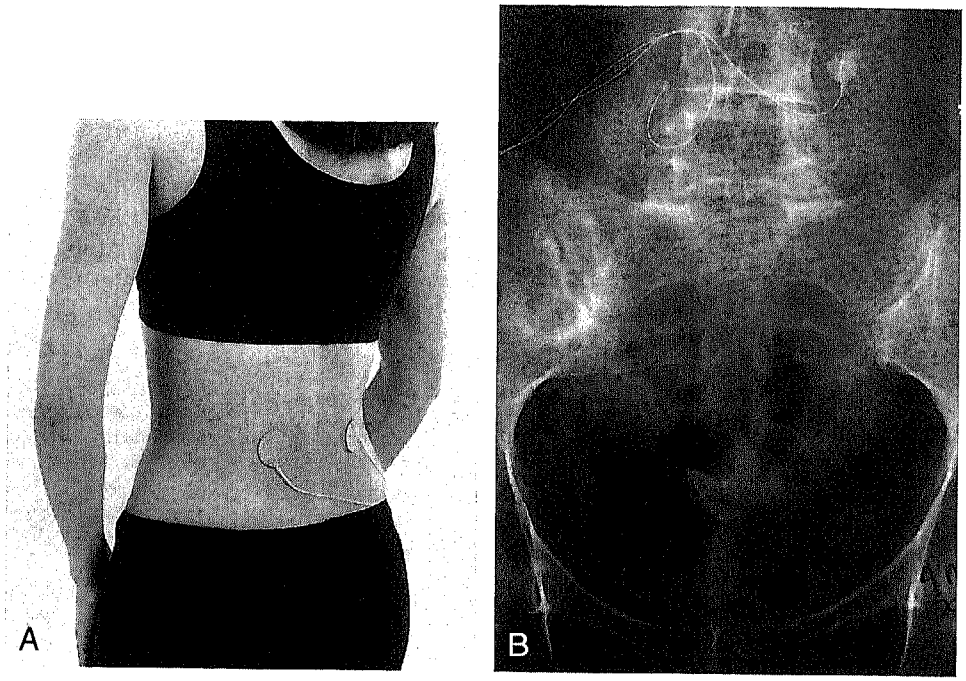

Figure 1. **A,** Capacitively coupled stimulation surface electrodes in position. **B,** Radiograph showing the position of skin electrodes (as indicated by the metal button connectors) relative to the fusion mass.

with a symmetric sine wave signal at 60 kHz using a pair of electrodes placed 10 cm apart and centered over the spine at the level(s) to be fused will produce the aforementioned current density and field in the vertebrae and the fusion mass. For this electrode location, the current density will be higher at the site of a posterolateral fusion mass than in the interspace where graft is placed for an interbody fusion. Figures 1A and 1B illustrate the location of stimulation electrodes on the skin relative to the fusion mass.

Previous studies have identified several factors that reduce fusion rates and clinical outcomes. Brown[12] identified the significant effect of smoking, and Turner[40] reported a trend in the literature suggesting that multilevel fusions have been associated with poorer outcomes. The use of internal fixation for patients with degenerative disc disease also is controversial, with some recent reports raising doubts about the clinical benefits.[18,20,26,42] Prior bone healing stimulation studies have not addressed the full range of fusion procedures nor the potential confounding factors of smoking, multilevel fusions, and internal fixation.

In his report on PEMF stimulation, Mooney[33] pointed out that not all radiographic fusion successes led to improved clinical results, and that some clinical successes occurred despite radiographic evidence of pseudarthrosis. This lack of perfect correlation between fusion and clinical success suggests that caution should be exercised in judging results based on either individual parameter. Turk and Rudy[39] discussed other sources of potential evaluation errors in their review article. Randomization is cited by these authors as the most effective method for minimizing the selection and evaluation biases of the surgeon, radiologists, and patients.

■ Methods

The current authors' hypothesis was that capacitively coupled stimulation would increase the rate of fusion and thus improve patient outcomes. This large multicenter trial captured data on stimulation used in combination with the various indications, procedures, bone graft materials, and internal fixation strategies encountered in contemporary practice. To improve scientific validity, the study was structured as a placebo-controlled, double-blind randomized trial with independent radiographic review. All investigators obtained permission to participate from an institutional review board, and the study was conducted under a Food and Drug Administration investigational device exemption.

The study was designed to include adult patients with primary lumbar fusions in the following clinical range: one- or two-level fusion; posterior lumbar interbody fusion (PLIF group), anterior lumbar interbody fusion (ALIF group), or posterolateral fusion; autograft, allograft, or a mixture of graft materials; and any type of internal fixation except interbody fusion cages (which were investigational during the protocol development period). Exclusion criteria eliminated patients with spinal pathologic processes including tumors or infection, spinal fractures, or systemic disease such as diabetes or osteoporosis that might affect fusion.

Patients were informed that this study was a randomized trial involving placebo stimulators. The active and placebo stimulators were provided by the manufacturer (Biolectron) at no charge. Patients could withdraw voluntarily after treatment was initiated or be dropped from the study by their surgeon because of noncompliance (*e.g.*, failure to return for follow-up or failure to use the device), relocation to another area, presence of a significant but unrelated condition, or pregnancy. Patients were given a small financial incentive to return for follow-up visits.

The patients were randomized within 3 weeks of the fusion surgery. They were instructed to use the stimulator 24 hours

Table 1. Patient Evaluation and Definitions of Success

Category	Reviewer	Score	Evaluation	Definition
Radiographic ALIF/PLIF	Investigator + blinded independent radiologist*	i	Success	>75% assimilation of graft and vertebrae
		ii	Success	50–75% assimilation of graft and vertebrae
		iii	Failure	25–50% assimilation of graft and vertebrae
		iv	Failure	<25% assimilation of graft and vertebrae
Radiographic posterolateral	Investigator + blinded independent radiologist*	i	Success	Fusion
		ii	Failure	Incomplete fusion
		iii	Failure	Absence of fusion mass
Clinical	Investigator	Excellent	Success	Resumption of normal activities; no pain or medication
		Good	Success	Resumption of normal to modified activities; occasional episodes of back or leg pain; occasional pain medication
		Fair	Failure	Resumption of activities on a limited basis; daily back and/or leg pain; requires frequent pain medication
		Poor	Failure	Unable to resume normal or modified activities; severe back and/or leg pain; requires daily pain medication

* Disagreements on radiographic success were resolved by a second blinded independent reviewer.

per day until healing occurred, or for 9 months if healing was delayed. The electrodes were placed on either side of the lumbar spine, approximately 10 cm apart at the level of the center of the fusion mass. Placebo stimulators were programmed so that patients with these disabled units received no therapy. If the stimulation was discontinued at 9 months without fusion, the patient returned at 12 months for a final clinical and radiologic evaluation.

Although patients were instructed to use the stimulator constantly, previous studies of capacitively coupled stimulation for nonunion fractures suggested that the actual daily use would be lower. A physician test meter was used to measure patient usage, recording the number of hours of stimulation that occurred between follow-up visits. The surgeon calculated and recorded the average usage hours per day at each patient visit. The stimulator automatically checked whether the electrodes were on the patient and whether the stimulator output was in the desired range, without revealing whether the device was the active or placebo version. An alarm sounded if the electrodes were not attached or the batteries were too weak to produce a proper therapeutic signal.

The criterion for overall success was stringent, requiring that radiographic and clinical results had been successful. Radiographic fusion alone or clinical good-to-excellent results alone led to an overall rating of failure in this study. This success criterion was chosen by the study designers because the hypothesized mode of action was enhancement of fusion, whereas the ultimate goal was clinical success. Radiographic success without clinical benefit is unsatisfactory to the patient, and clinical improvement without radiographic fusion may not be attributable to the stimulator. Data on radiographic and clinical results were collected. These are reported separately for comparison with prior reports on bone growth stimulation in the medical literature.

The combined success measure also allowed stratification analysis that included both radiographic and clinical success. Previous study reports on PEMF[33] and DC[25] technologies provided stratification only on radiographic results.

The method of evaluation used in the current study is described in Table 1. Radiographic success for posterolateral fusions was defined prospectively as follows:

> Fusion success required the presence of mature-appearing, uninterrupted bony masses bilaterally at the fusion levels, ideally on both anteroposterior and lateral radiographs. If lateral flexion, neutral, and extension views were submitted, the images were superimposed and judged for total lack of movement. If orthopedic hardware was present, there could not be any lucency or motion around the screws.
>
> Incomplete fusion was marked by immature-appearing bone mass on either side, lack of a bone mass on one side, or lack of continuity in the bone mass on either side. Any evidence of motion or lucency around internal fixation hardware also was a sign of incomplete fusion.
>
> Absence of fusion mass was defined as complete resorption of the graft.

At the final follow-up visit, patients were categorized as fused or not fused. Incomplete fusion was classified as not fused.

The rating of clinical success also was defined prospectively, with success requiring resumption of normal or modified activities, no pain or occasional pain, and no medication or occasional medication.

A retrospective telephone survey was conducted with patients who had at least 2 years follow-up to obtain information that was not requested on the initial patient case report form and to answer a question that arose during preliminary data review. Patients were asked whether they were receiving workers' compensation disability payments during their participation in the study. They also were asked whether they had undergone subsequent back surgery.

The statistical measure of significance used in this report was the Yates corrected chi-square test, which is more conservative than other tests used for significance analysis. As an example, the following P values were derived in comparing success rates for active and placebo patients with degenerative disc disease: Pearson chi-square, $P = 0.0008$; Fisher's exact test (one tail), $P = 0.0007$; Fisher's exact test (two tail), $P = 0.0012$; and Yates corrected chi-square test, $P = 0.002$. This conservative analysis method was used to make sure that the conclusions were statistically valid.

■ Results

From August 1992 to January 15, 1997, 24 investigators enrolled 337 patients. At the time of this analysis, 34 patients were still wearing the device and 20 pa-

Table 2. Patient Demographics and Other Information

	Active	Placebo
Females [no. (%)]	37 (43.5)	45 (47.9)
Males [no. (%)]	48 (56.5)	49 (52.1)
Age (mean) (yr)	45	40
Age range (yr)	21–76	22–73
Height (female) (cm)	163	165
Height (male) (cm)	180	178
Weight (female) (kg)	67	66
Weight (male) (kg)	88	84
Nonsmoker [no. (%)]	60 (70.6)	68 (72.3)
Smoking [no. (%)]	25 (29.4)	26 (27.7)

tients had missing documents, making final determination of status impossible. An additional 63 patients withdrew or were dropped from the study by their surgeons: 27 for noncompliance (failure to wear the device or return for follow-up visits), 9 for adverse reactions (all skin irritation), 1 for wound infection, 6 for protocol violations by the surgeon, 6 for relocation, and 14 for voluntary reasons. The study is ongoing, with 220 patients having completed final status documents. Of these patients, 179 also have completed independent radiographic review. These latter patients comprise the group analyzed in this article.

Study centers contributed from 2 to 56 patients, with the largest center contributing 14% of the 220 patients who completed the treatment, having final status forms. Table 2 summarizes important demographic characteristics of the 179 patients with final status forms and independent radiographic review. Table 3 shows a breakdown of the 179 clinical subjects with complete records

Table 3. Patient Diagnosis and Surgical Procedures: No. (%)

	Active	Placebo
Diagnosis*		
Degenerative disc disease only	52 (61.2)	54 (57.4)
Herniated disc	25 (29.4)	31 (33.0)
Spondylolisthesis	24 (28.2)	30 (31.9)
Degenerative arthritis	6 (7.1)	4 (4.3)
Inflammatory arthritis	0	0
Previous surgery		
Laminectomy	15 (17.6)	27 (28.7)
Discectomy	17 (20.0)	21 (22.3)
Type of fusion†		
Anterior interbody (ALIF)	14 (16.5)	18 (19.1)
Posterior interbody (PLIF)	18 (21.5)	30 (31.9)
Posterolateral	61 (71.8)	62 (66.0)
Range of fusion		
L3–L4	5 (5.9)	5 (5.3)
L3–L5	5 (5.9)	9 (9.6)
L3–S1	2 (2.4)	1 (1.1)
L4–L5	19 (22.4)	20 (21.3)
L4–S1	30 (35.3)	33 (35.1)
L5–S1	24 (28.2)	26 (27.7)
Use of internal fixation		
Internal fixation	65 (76.5)	67 (81.9)
No internal fixation	20 (23.5)	17 (18.1)

* Patients could have more than one indication.
† A total of 14 patients had ALIF or PLIF fusions combined with posterolateral fusions.

Table 4. Success Rating (Final Evaluation) With Stratification by Fusion Procedure

	Active	Placebo	*P* Value†
n*	85	94	
Clinical and radiographic success (%)	84.7	64.9	0.0043
Clinical failure, radiographic failure, or both failed (%)	15.3	35.1	

Stratification Group	n	Active Success‡ (%)	Placebo Success‡ (%)	*P* Value
Posterolateral fusion	109§	89.1	64.9	0.006
ALIF/PLIF fusion	56§	79.2	68.8	NS

* n = total subjects (success + failure) in the group.
† Yates corrected chi-square test.
‡ Both radiographic and clinical success.
§ A total of 14 patients had combined ALIF/PLIF and posterolateral fusions; they are not considered in this stratification.
NS = not significant.

in terms of diagnosis, type of fusion, level of the spine fused, and use of internal fixation. Some surgeons chose internal fixation for all their patients undergoing fusion. Others used internal fixation part of the time, and still others never used fixation. The similarity of the active and placebo groups indicates that the randomization process was extremely effective.

Active patients used the capacitively coupled stimulator an average of 15.7 hours (range, 1.7–23.4 hours). Placebo patients used their disabled stimulators an average of 16.5 hours (range, 1.3–23.7). These data strongly suggest that the patients could not determine the group to which they were randomized, confirming that there was no difference between the groups in terms of average usage.

Table 4 lists success rates for the active and placebo patients, with stratification by type of fusion procedure. To be rated a success, the patients had to have a solid fusion and a good or excellent clinical result. The success ratings showed a highly significant difference between active and placebo groups: 84.7% and 64.9% success, respectively ($P = 0.0043$). There was significant benefit for posterolateral fusions ($P = 0.006$), but the smaller ALIF/PLIF group did not reach significance.

For a better understanding of the results, stratification analysis was performed to examine the impact of the type of fusion procedure, smoking, use of internal fixation, and single- *versus* two-level fusions. These factors are summarized in Table 5. Every comparison demonstrated a superior success rate for stimulation, but many of the smaller strata had insufficient numbers of patients to prove significance. Capacitively coupled stimulation had more impact on patients with degenerative disc disease (86.5% success *versus* 57.4% for placebo patients; $P = 0.002$), whereas there was less difference for patients with a diagnosis of degenerative disc disease and a herniated disc. There was a trend toward significance for patients with degenerative disc disease and spondylolis-

Table 5. Stratification of Results by Previous Surgery, Indication, Smoking Status, Number of Levels Fused, and Use of Internal Fixation

Stratification Group	n*	Active Success (%)	Placebo Success (%)	*P* Value
Prior surgery				
Laminectomy	42	80.0	55.6	NS
Discectomy	38	64.7	47.6	NS
Indication†				
Herniated disc	56	72.0	64.5	NS
Spondylolisthesis	54	91.7	66.7	0.062
Degenerative disc disease	113	87.5	59.7	0.002
Smoking status				
Smokers	45	69.6	50.0	NS
Nonsmokers	134	84.7	69.4	0.006
Number of levels fused				
Single level fusion	99	85.4	66.7	NS
Multiple levels	80	83.8	62.8	NS
Use of internal fixation				
Internal fixation	142	81.5	61.0	0.013
No fixation	37	95.0	82.4	NS

* n = total subjects (success + failure) in the strata.
† Patients could have more than one indication. Success rates include all patients with a mention of this indication.
NS = not significant.

thesis (91.7% success *versus* 66.7% for placebo patients; $P = 0.063$).

As previously described in the literature, smoking has a striking effect on patient results. Of all the stratifications, the combined smoking and placebo group had the worst results (only 50% success). Smoking patients with active stimulators fared nearly 20% better, but this was not statistically significant, possibly because of low numbers in the smoking group. The results for all smokers (actives plus placebos) were significantly worse than for nonsmokers ($P = 0.02$).

Patients with internal fixation appeared to have significant benefit from the addition of capacitively coupled stimulation (82% success *versus* 61% for nonfunctional units; $P = 0.02$). Table 6 describes the internal fixation strata further subdivided to show the coexisting impact of multilevel fusions and smoking on physician-reported success rates. The addition of stimulation appeared to improve the results obtained with internal fixation across the smoking and multilevel substrata. However, only the larger patient groups reached statistical significance. When two-level fusion with patients who have fixation is compared, actives had an 84% success rate, whereas placebo patients had a 58% success rate ($P = 0.04$). Nonsmokers with fixation had an 89% success rate with active stimulation *versus* 67% with placebos ($P = 0.02$).

In a follow-up blind telephone survey, the authors were able to contact 119 of 208 patients with more than 2 years follow-up. This group reported that there were 34 additional operations, which occurred primarily in the internal fixation subgroup. Approximately 33% of the patients with internal fixation had a subsequent back surgery compared with 13% of the patients without fixation. Half of the subsequent procedures in the internal fixation group were for hardware removal. There was no significant difference in reoperation rates between active and placebo patients in the internal fixation group or the no fixation groups. Randomization for workers' compensation also was checked for effectiveness. Randomization appears to be uniform, with 27% of telephone survey respondents in the active group and 35% in the placebo group reporting that they received compensation.

■ Discussion

The data in Tables 4 and 5 are striking in that all comparisons show an advantage for active stimulators over placebo units. The authors believe that clinical improvement and radiologic evidence of fusion are required for a fusion adjunct to be considered a success. According to these criteria, capacitively coupled stimulation had a significant positive effect on success rates for lumbar spine fusions. The large patient group enrolled in this study allowed some degree of stratification for comparing the effects on posterolateral and interbody fusions. Because this study included a broad spectrum of indications and fusion adjuncts, it also provided interesting information about the impact of internal fixation on fusion.

Conducting a placebo-controlled randomized trial poses many challenges. Besides the difficulties in finding patients willing to participate, there is some difficulty in convincing patients to complete a study that requires

Table 6. Internal Fixation Impact Stratifications: Smoking and Levels Fused

	No Internal Fixation				Internal Fixation			
	Active Stimulation		Placebo Stimulation		Active Stimulation		Placebo Stimulation	
	n*	Success (%)	n*	Success (%)	n*	Success (%)	n*	Success (%)
Levels fused								
1 level	14	100	12	75	34	79	39	64
2 levels	6	83	5	100	31	84	38	58
Smoking status								
Smokers	2	100	5	80	21	67	17	41
Nonsmokers	18	94	12	83	44	89	60	67

* n = total subjects (success + failure) in the substrata.

Table 7. Impact Stratifications: Posterolateral vs. Interbody Fusion

Fusion Procedure	n	Parameter	Active Success (%)	Placebo Success (%)	*P* Value
Total study	179	Clinical + radiological	84.7	64.9	0.004
		Clinical	88.2	75.5	0.046
		Radiological	90.6	81.9	NS
Posterolateral	109	Clinical + radiological	89.1	64.8	0.006
		Clinical	92.7	79.6	0.088*
		Radiological	92.7	75.9	0.013
ALIF or PLIF	56	Clinical + radiological	79.2	68.8	NS
		Clinical	79.2	75.0	NS
		Radiological	87.5	93.8	NS
ALIF or PLIF + posterolateral	14	Clinical + radiological	66.7	50.0	NS
		Clinical	83.3	50.0	NS
		Radiological	83.3	75.0	NS

* *P* values between 0.05 and 0.10 show a trend toward statistical significance.
NS = not significant.

daily device use for as long as 9 months. Because both functional and placebo stimulators produced no sensation, some patients felt that their unit was providing no benefit and stopped participating in the study. Fourteen (4.2%) of the initial 337 patients withdrew. In addition, 27 patients were judged to be noncooperative by their surgeons. Altogether, 40 patients (approximately 12%) could not be analyzed. This dropout rate is similar to the 20% withdrawal rate cited by Mooney[34] in a preliminary PEMF clinical study presentation, and lower than the range described for voluntary contraceptive devices (23–45%), which also require patient participation over an extended period.[38]

Mooney[33] observed that 35% of the study subjects used the PEMF device inconsistently (fewer than 4 hours per day), producing results similar to those of placebo patients. The inconsistent patients were excluded from further analysis in the Mooney article. In the current study, all patients with complete records were analyzed whether they used the device as recommended or not. No trends could be identified that related success rate to average hours of use. With capacitively coupled stimulation technology, there appears to be a low threshold for stimulation effectiveness, well below the typical usage chosen by the study participants.

There was a small number of device-related withdrawals (9 patients or 2.6%) because of adverse effects, all caused by skin irritation from surface electrodes. These adverse effects were concentrated in the early portion of the study. The introduction of hypoallergenic hydrogel electrodes essentially eliminated skin irritation as a cause for discontinuation.

Separately, the clinical success rates were 88.2% (active group) and 75.5% (placebo group) ($P = 0.034$), and the radiographic fusion rates were 90.6% (active group) and 81.9% (placebo group) ($P = 0.1454$, not significant). In the total group, there was a greater difference between the clinical outcomes of the active and placebo groups than between the radiographic fusion rates of the two groups. When the data is stratified by type of procedure (Table 7), it reveals a significant benefit to patients with posterolateral fusion in radiographic fusion and a trend toward significance for clinical success rates. The benefit for the ALIF/PLIF group did not reach clinical significance because of the smaller number in this stratification group.

The impact of internal fixation is difficult to evaluate in this type of broad study. The state of the art was evolving rapidly, and surgeons were free to choose any fixation system. No attempt was made to determine the individual investigator's experience with internal fixation. Possibly some were early in the learning curve with their choice of system. There also was a wide range of underlying instability. Some were patients with degenerative disc disease who were quite stable, whereas others had significant destabilizing decompressions for spinal stenosis.

The study was not designed to evaluate the performance of internal fixation systems, but it did raise some questions about their effectiveness. Although each investigator's decision criteria for using internal fixation is not known, it is reasonable to assume that internal fixation generally was used in more complicated instability cases. In the current study, it appears that radiographic fusion and successful clinical results were at least delayed, and possibly reduced, compared with the results in patients who had no adjuncts, and especially in patients who had capacitively coupled stimulation. This observation is consistent with findings in several recent comparative outcomes studies that could not demonstrate a significant clinical benefit for internal fixation.[18,20,26,42]

Ito[23] also observed lower fusion rates with internal fixation than without fixation in a canine PEMF study. The capacitively coupled stimulation study was not designed to evaluate radiographic fusion rates in the long term. Radiographic fusion rates for patients with internal fixation might increase with a longer follow-up period. However, average clinical outcomes do not seem to improve beyond 6 months for patients with internal fixation, as observed by Zdeblick[42] and Katz.[26] In the current study, clinical and radiographic results had to be positive for the fusion to be considered a success. For

these reasons, it is the authors' observation that internal fixation has a lower impact than expected.

The unexpected results in patients who underwent internal fixation and their improvement with the addition of capacitively coupled stimulation may have an explanation at the cellular level. Electricity in its various forms can alter many cellular events.[6] Numerous studies have shown that bone cells exposed to an appropriate electric field respond with an increase in proliferation as measured by an increase in deoxyribonucleic acid (DNA) content or an increase in [^{3}H]thymidine/DNA incorporation.[2,8,21,27,35] Other studies have evaluated signal transduction mechanisms that mediate the bone cell's response to electrical stimulation. Cyclic adenosine monophosphate,[1,2,7,16,21,22,27,28,31] cytosolic calcium,[15,36,41] and prostaglandin E_2 (PGE_2)[30] all have been implicated as secondary messengers in the signal transduction occurring when bone cells are exposed to electricity in its various forms.

Recently, it was concluded that the bone cell's response to a capacitively coupled sine wave signal at 60 kHz (output of 44.8 volts; induced field of 20 mV/cm with a current density of 300 $\mu A/cm^2$) was mediated by transmembrane calcium translocation via voltage-gated calcium channels, increase in intracellular calcium, activation of phospholipase A_2, and a subsequent increase in PGE_2.[30]

Other studies have examined the effects of various forms of electricity on local growth factors. For example, it has been shown that a capacitively coupled signal of the same electric field described earlier led to an increase in the level of transforming growth factor beta 1 (TGF-β1) mRNA in bone cells by a mechanism involving the calcium–calmodulin pathway.[43]

These TGF-β studies may hold the clue to the improved results seen with the combination of capacitively coupled stimulation and internal fixation. After a fracture, TGF-β increases dramatically in proliferation osteoblasts in the subperiosteal callus.[23,43] Mechanically strained bone cells show an increase in TGF-β1 mRNA.[44] The current authors hypothesize that internal fixation causes stress shielding (and perhaps a decrease in TGF-β), and that the capacitively coupled electrical signal reverses the effects of stress shielding by producing a local increase in TGF-β.[32,37]

Although this capacitively coupled stimulation study yielded significant new information supporting use of the technology for selected patients undergoing fusion, it had some weaknesses. This study did not collect pretreatment clinical data, nor did it include validated patient-reported outcomes measures such as those obtained by the North American Spine Society low back pain outcome assessment instrument. This study also was quite complex, with a large array of indications and procedures. Some surgeons chose internal fixation for all their patients undergoing fusion, whereas others never used fixation. A simpler study could have led to stronger conclusions over a narrower range of variables. Finally, the impact of workers' compensation and the incidence of subsequent surgery were not examined prospectively. The use of a follow-up survey did not exclude the possibility of selection bias because it was not possible to contact all patients with 2-year follow-up.

Future plans for this clinical study include completion of enrollment and follow-up so that a larger number of patients can be analyzed. The complete study database will be subjected to logistic regression analysis for further investigation of the impact exerted by such variables as the type of fusion procedure, the use of internal fixation, single- *versus* two-level fusions, smoking, prior surgery, and the like.

The study produced significant evidence to justify a direct cost-effectiveness study of capacitive coupled stimulation with and without internal fixation for posterolateral fusions. The telephone survey suggested that patients with internal fixation have a higher rate of subsequent surgical procedures after the primary fusion. A prospective cost-effectiveness study with a consistent protocol for use of internal fixation and with longer-term follow-up could clarify this issue. A secondary objective for a cost-effectiveness study could be to determine whether earlier return to work is possible with capacitively coupled stimulation and internal fixation, which could offset the higher expense of repeat surgeries associated with internal fixation.

In conclusion, this study produced clear evidence of benefits from capacitively coupled stimulation:

There were no serious complications, and the active stimulation patients received benefits over a wide range of average daily hours of use.

The greatest improvement came when capacitively coupled stimulation was used on posterolateral fusions.

This stimulation seems to be useful for patients with internal fixation who have had a low fusion rate because of underlying instability, poorly understood effects of internal fixation such as the biochemical events associated with stress shielding, or both.

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