A Randomized Double-Blind Prospective Study of the Efficacy of Pulsed Electromagnetic Fields for Interbody Lumbar Fusions

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A randomized double-blind prospective study of pulsed electromagnetic fields for lumbar interbody fusions was performed on 195 subjects. There were 98 subjects in the active group and 97 subjects in the placebo group. A brace containing equipment to induce an electromagnetic field was applied to patients undergoing interbody fusion in the active group, and a sham brace was used in the control group. In the active group there was a 92% success rate, while the control group had a 65% success rate ($P > 0.005$). The effectiveness of bone graft stimulation with the device is thus established. [Key words: lumbar interbody fusion, pulsed electromagnetic field, fusion rate]

LUMBAR FUSIONS with or without internal fixation are slow to achieve total union and the success rate still remains unpredictable. The interbody fusion is attractive, but incorporation to achieve solid union is slow. Because of the anatomic setting, there is a wide avascular space between the vertebral bodies. Although the bone graft is typically under compression loading, revascularization and, thus, ossification of the bone graft takes many months. Some of the problems in using lumbar fusions and specifically interbody fusions are because of this phenomenon.

Certainly it is reasonable from a clinical standpoint to search for mechanisms that might enhance the rate and percentage of success of interbody lumbar fusions.

BACKGROUND

What can be done to enhance the biologic factors that control the rate of fusion? In the 1960s it was discovered that mechanical stresses generated electrical potentials in bone.[3,12] Thus it seemed reasonable to assume that manipulation of electrical energy might enhance bone repair. Bassett later demonstrated this.[4] Finally by the mid 1970s, electrical energy in the form of electromagnetic fields was demonstrated to accelerate bone repair.[5]

The efficacy of this form of bone stimulation remained controversial in the area of fracture repair because of the great difficulty of providing matched fractures in a real-life setting. Although it appeared to be successful in homogeneous patient populations,[10,13,24] it was very difficult to draw a solid conclusion because of the relatively small numbers, which did not allow statistical interpretation.[21] Eventually, a good model emerged for fracture healing in the form of comparison of a standardized operation. Intertrochanteric osteotomy provides such a model. Recently, Borsalino et al[7] demonstrated that pulsed electromagnetic fields in a double-blind prospective study of 32 consecutive patients showed a statistically significant different ($P > 0.01$) between controls in stimulated patients. In this series, a blinded observer read the roentgenograms of the intertrochanteric osteotomies at 40 and 90 days after osteotomy. Criteria for union was 50% obliteration of the osteotomy site. This study had the advantage of unbiased radiographic reading of a standardized surgical procedure at standardized times postsurgical time.

Although direct current stimulation has been demonstrated to enhance fusion,[9,17] these studies were neither blinded nor strictly randomized. The potential advantage of pulsed electromagnetic fields for the achievement of enhanced lumbar fusion certainly is apparent in that the direct current devices are invasive and potentially require removal of the stimulating device, which is an additional disadvantage. Kahanovitz[16] performed a series of lumbar fusions on dogs and demonstrated an enhanced rate of early repair but could not demonstrate an ultimately higher success rate of fusion at 15 weeks. The results were based on histologic as well as radiographic evaluation. Rate of new bone formation, of course, is extremely difficult to monitor, even histologically. Quantification of bone formation requires standardization of evaluation and test situations.

At our laboratories at the University of Texas Southwestern Medical School in Dallas, a system of quantitative analysis of new bone formation was developed.[14] This system used an osteoconductive lattice of porous hydroxyapatite (HA). This structure was made from sea coral. This form is a very consistent structure and thus offers a standardized framework. In addition, quantitative morphometry using back scatter scanning electron microscopy was used for objective evaluation. With this method, the density of new bone versus implant versus soft tissue or void space could be differentiated. The density specific images were digitized and counted by computer. This resulted in a quantitative measure of the percentage of new bone versus implant versus soft tissue space. Also the boundary fraction could be determined, ie, the percentage of implant covered by new bone. With this method it was possible to determine the efficacy of various types of bone substitutes.[22]

Because of the potential for very precise quantification of the rate of new bone formation, this appeared to be an excellent model to evaluate adjuncts to bone formation. Thus this study was initiated, which compared bone in-growth into porous structures under the influence of pulsing electromagnetic fields.[22] In this study, rabbits were placed in plastic cages with a pair of parallel transducers placed around the plastic cage for 8 hours. A magnetic field of 1.8 gauss with a frequency of 1.5 Hz. was used. The control rabbits were placed in similar plastic cages remote from the electromagnetic fields. Three millimeter diameter

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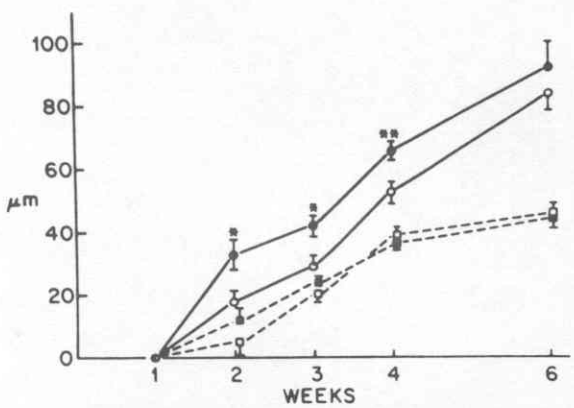
implants were placed into the tibia of the animals. Each tibia had a hydroxyapatite implant and tricalcium phosphate implant. The tricalcium phosphate implant had a much smaller pore size. The specimens were obtained at 1, 2, 3, 4, and 6 weeks after surgery. Previous experience had identified that maximum amount of new bone formation in this specific model was achieved in rabbits at 6 weeks.

As noted in Figure 1, a volume fraction of bone was significantly greater in the implants of animals receiving pulsed electromagnetic field treatment. The same was true of the mean trabecular thickness of new bone. Interestingly, there was no affect on implants of tricalcium phosphate with the diminished pore size. The pores of the hydroxyapatite (Interpore International, Inc., Irvine, CA) average 600 μm in diameter with interconnections averaging 260 μm in diameter. The tricalcium phosphate pores measured 100–300 μm with inconsistent interconnections. The effect of pulsed electromagnetic fields thus appeared most beneficial early in the healing phase. Certainly by this well-controlled study, a definite effect of pulsed electromagnetic fields could be identified.

Because of the demonstration of positive affect by this controlled study, it seems reasonable to progress into clinical application of this noninvasive method. On this basis, a protocol for clinical application was developed in cooperation with American Medical Electronics. It was recognized from the beginning that this study would have to be a prospective blinded study in an effort to offer scientific credibility to the application of pulsed electromagnetic fields. The only method of evaluation by a multicenter study would be radiographic. It was recognized that radiographic criteria were extremely difficult to standardize. Interbody fusions at least have greater potential for repeatable radiographic evaluation as to union status compared with posterior or posterolateral fusions. It was recognized that a more ideal method of union evaluation would be range-of-motion films. It seemed impossible to assume a standardized method of range-of-motion, which would be comparable in the many centers to be used for this procedure. It was hoped that the use of blinded observers would offer at least a standardized method of radiographic reading.



Mean trabecular thickness of new bone in the cortical window area. Vertical bar: mean width of bone trabeculae (μm). Horizontal bar: postoperative period (weeks). Hydroxyapatite (HA) in the pulsing electromagnetic field (PEMF) group (●---●). HA in the control group (○---○); TCP in the PEMF group (■---■); TCP in the control group (□---□). Results are expressed as the mean ± SEM. Stimulated HA demonstrated significant differences from the control HA at $^{*}p < 0.025$ and $^{**}p < 0.01$ by nonparametric analysis and Welch's approximation to the *t* test.

Fig 1. Bone ingrowth into porous hydroxyapatite with and without PEMF.

MATERIALS AND METHODS

Surgeons familiar with interbody fusions were recruited for this project. In the group of patients who would receive a nonfunctioning brace, institutional review boards of the various cooperating institutions insisted that the patients be aware of this when they agreed to participate. It was inappropriate to ask insurance companies to pay for potentially nonoperating electromagnetic field braces. The equipment was therefore donated by the manufacturer. The number of cases each surgeon contributed to this study are listed in Table 1.

Patients included in this study were adults of either sex undergoing initial attempts at interbody spinal fusion either from an anterior or posterior approach. Candidates were excluded if they presented with trauma, inflammatory conditions of the spine, severe osteoporosis, or metabolic problems such as diabetes, renal dysfunction, or metastatic cancer.

After surgery, patients were fitted with a special brace with electromagnetic coils, which they were instructed to wear at least 8 hours a day. Neither the patient nor the surgeon was aware of the functioning characteristics of the brace. They were aware, however, that the brace itself may or may not be functioning. The patients were not aware that the amount of usage was monitored by the brace.

Success criteria were based on radiographic evaluation. A fusion was defined as solid if it was more than 50% assimilated. The surgeon identified the radiographic status at the time of union, but an independent blinded radiologist confirmed this reading. In cases where a disagreement between the clinician and radiologist occurred, an independent blinded orthopaedic surgeon acted as the third reviewer. The investigators' diagnosis of failure was never allowed to be overruled by the independent review. In an arthrodesis spanning 2 segments, both levels had to be graded as solidly fused for the patient to be classified as a success.

Safety was evaluated on the basis of the incidence of subject complaints and adverse reactions. In addition, the clinician identified whether the clinical result was excellent, good, fair, or poor. Other characteristics such as disability time before surgery, smoking, numbers of previous surgeries, and graft type were recorded.

RESULTS

A total of 195 patients completed this study. There were 98 patients in the active group and 97 patients in the placebo group. In that the braces

Table 1. Participating Surgeons Ranked by Number of Cases Contributed <3

Number of cases	*Surgeon*
59	A
26	B
19	C
17	D
12	E
11	F
11	G
9	H
9	I
7	J
5	K
4	L
3	M
2	N
2	O
2	P
1	Q
1	R
1	S
1	T
1	U
1	V
1	W
1	X

were constructed to monitor usage, those with inconsistent use (< 8 hours a day) could be identified compared with those with consistent use. Table 2 demonstrates the success rate. In those 64 patients randomized to the active group who consistently used the device, there was a 92.2% success rate. In those patients who were inconsistent (< 4 hours use a day) in the use of the equipment, there was a similar success rate to the placebo group, which had an overall success rate of 64.9%. Originally there were 107 patients in the active group and 99 patients in the placebo group. Reasons for disqualification were three patients for medical reasons in the active group, and one in the placebo group. Three patients in the active group and one patient in the placebo group did not have an interbody fusion. One active patient did not finish the study because of alcohol dependency. Two patients had surgical complications that required revision and two active patients required repeat surgery for continued degenerative disease. Four patients in the active group were lost to follow-up.

The type of grafts used for the interbody fusion apparently made no difference in rate of success. Autogenous iliac crest graft compared with cadaver allograft gave similar results. About the same numbers of graft types were used in each group (Table 3). Internal fixation might be expected to make a difference, but not apparently in the active group (Table 4). There was a possible effect in the placebo group, but the numbers were too small to be statistically significant and the types of internal fixation were too varied to offer any conclusions. One factor that has been suggested to be a deterrent to fusion—smoking—made no statistical difference in the success rate, although there was a slight trend (Table 5).

Preoperative diagnosis was quite varied, as noted on Table 6. Although internal disc disruption and spondylolisthesis had the best results in the active group, there was no statistical difference when compared with the other diagnoses (Table 6). Single level procedures did slightly better than double level procedures in both groups, although this was not statistically significant (Table 7). Age and sex made no difference. There were 59 men and 48 women enrolled in the active group, and 52 men and 47 women enrolled in the placebo group. The active group averaged 37.9 years of age and the placebo group averaged

Table 2. Randomized Double-Blind Phase Results by Consistent Use versus Inconsistent Use

	Active group			Placebo group		
Category	*Total number*	*Total healed*	*Success rate*	*Total number*	*Total healed*	*Success rate*
Consistent use	64	59	92.2%	53	36	67.9%
Inconsistent use	34	22	64.7%	44	27	61.4%
Total	98	81	82.7%	97	63	64.9%

Table 3. Randomized Double-Blind Phase Results by Graft Type

	Active group			Placebo group		
Graft type	*Total number*	*Total healed*	*Success rate*	*Total number*	*Total healed*	*Success rate*
Autogenous	25	23	92.0%	19	14	73.7%
Cadaverous	27	25	92.6%	22	16	72.7%
Autogenous/cadaverous	12	11	91.7%	12	6	50.0%
Total	64	59	92.2%	53	36	67.9%

Table 4. Randomized Double-Blind Phase Results by Internal Fixation

	Active group			Placebo group		
Internal fixation	*Total number*	*Total healed*	*Success rate*	*Total number*	*Total healed*	*Success rate*
No fixation	16	15	93.8%	14	8	57.1%
Fixation	48	44	91.7%	39	28	71.8%
Total	64	59	92.2%	53	36	67.9%

Table 5. Randomized Double-Blind Phase Results by Smoking

	Active group			Placebo group		
Smoking	*Total number*	*Total healed*	*Success rate*	*Total number*	*Total healed*	*Success rate*
No smoking	37	35	94.6%	33	24	72.7%
Smoking	27	24	88.9%	20	12	60.0%
Total	64	59	92.2%	53	36	67.9%

Table 6. Randomized Double-Blind Phase Results by Diagnosis

	Active group			Placebo group		
Diagnosis	*Total number*	*Total healed*	*Success rate*	*Total number*	*Total healed*	*Success rate*
Herniated nucleus pulposus	20	17	85.0%	17	13	76.5%
Spondylolisthesis	4	4	100.0%	5	4	80.0%
Degenerative disc disease	19	17	89.5%	13	8	61.5%
Internal disc disruption	25	25	100.0%	23	15	65.2%
Failed fusion	1	0	.0%	1	1	100.0%
Stenosis	2	2	100.0%	1	0	.0%
Other	3	3	100.0%	1	1	100.0%

Table 7. Randomized Double-Blind Phase Results by Number of Fusion Levels

	Active group			Placebo group		
Fusion level	*Total number*	*Total healed*	*Success rate*	*Total number*	*Total healed*	*Success rate*
Single level	46	43	93.5%	40	29	72.5%
Double level	18	16	88.9%	13	7	53.8%
3 or more levels	0	0	.0%	0	0	.0%
Total	64	59	92.2%	53	36	67.9%

37.6 years of age at the start of treatment. The differential of age between older than 50 years and younger than 50 years offered no statistical significance. The duration of time before surgical care also offered no significant difference.

Thus, 92.2% of patients receiving active devices and using them consistently had a solid fusion as defined by blinded radiographic evaluation of the bone graft. Those in the placebo group fused at a rate of 67.9%. This is statistically significant at $P > 0.005$. Factors such as sex, age, fusion level, number of grafts, graft type, and internal fixation made no difference. Smoking made little difference.

Patient tolerance of the device was fairly good, although it was found to be uncomfortable and bulky by about 13% of the patients. Other factors were relatively insignificant (Table 8). There was some correlation between radiographic success and clinical success (Table 9). All patients had been evaluated a minimum of 12 months after surgery. Clinical characteristics at a longer follow-up were not tabulated. In the placebo group, certainly radiographic success correlated with a good result and radiographic failure correlated with a poorer result. However, the numbers were too small to offer statistical significance.

Table 8. Randomized Double-Blind Phase Safety by Patient Complaints

	Active group		Placebo group	
Category	*n*	*%*	*n*	*%*
None	90	84.1%	84	84.8%
Patient finds device bulky or uncomfortable	14	13.1%	13	13.1%
Minor skin rash	2	1.9%	0	0.0%
Insomnia	0	0.0%	0	0.0%
Pain while using device	1	0.9%	1	1.0%
Fainting	0	0.0%	0	0.0%
Nausea/diarrhea	0	0.0%	0	0.0%
Polymenorrhea	0	0.0%	0	0.0%
Other	0	0.0%	1	1.0%
Total	107	100.0%	99	100.0%

DISCUSSION

Pulsed electromagnetic fields have been applied with success to a wide array of physiologic healing problems. This seems to make a difference in neuroregeneration,[15,19] in healing of skin wounds,[20] and in the healing of ligaments.[11] It has been demonstrated to make a difference in human soft tissue healing such as epicondylitis[8] and in rotator cuff tendonitis.[6] Our own studies identified that the effect on bone healing occurs early in the healing phase. Whether this is due to stimulation of new blood supply is undefined.[23] Apparently there is an effect of revascularization in femoral head necrosis.[1,2] All of these studies confirm that there is a physiologic event related to pulsed electromagnetic fields.

An apparent confirmatory statistic of this study is the correlation with compliance and success. This specific factor may be an explanation for some blur in our understanding of the efficacy of the method. Certainly clinical compliance is often one of the most confounding features of therapeutic trials. The specific equipment used in this study allowed an evaluation of that aspect.

Certainly one might criticize this study for its failure to be more specific in the analysis of fusion. Given the scope of the project, however, there seems no other alternative than to rely purely on radiographic criteria. Even this is difficult in that obviously the quality of films from 24 different investigators cannot be uniform. The variability, however, should be canceled out with the use of a blinded observer with no knowledge of the surgeon or treatment method.

An investigation of the pulsed electromagnetic fields for pseudarthrosis has also been performed. This, of course, could not be a prospective double-blind study in that the surgical care had already been carried out. Nonetheless, patients could be randomized on the basis of consistent (< 8 hours a day) and inconsistent use. A group of 126 patients participated in a multicenter study.[18] In this study, 100 patients with consistent use had a 67% radiographic success (50% assimilation as defined by blinded radiologists). Inconsistent users had only a 19.2% success. In this group, there was a much closer correlation between smoking and nonsmoking and success. In this study, 67.2% of the consistent user successes were nonsmokers while 66.7% of the consistent user successes were smokers. The lack of greater success with the

Table 9. Randomized Double-Blind Phase Results by Clinical Assessment

	Active group				Placebo group			
	Radiographic success		Radiographic failure		Radiographic success		Radiographic failure	
Clinical assessment	n	%	n	%	n	%	n	%
Excellent	30	50.8%	1	20.0%	13	36.1%	3	17.6%
Good	21	35.6%	1	20.0%	18	50.0%	5	29.5%
Fair	5	8.5%	1	20.0%	5	13.9%	4	23.5%
Poor	3	5.1%	2	40.0%	0	.0%	5	29.4%
Total	59	100.0%	5	100.0%	36	100.0%	17	100.0%

Table 10. Randomized Double-Blind Phase Completed, Ongoing, Withdrawals, and Lost to Follow-up Subjects

	Active group		Placebo group	
Type	n	%	n	%
Completed				
Consistent use	64	59.8%	53	53.5%
Inconsistent use	34	31.8%	44	44.4%
Ongoing	0	0.0%	0	0.0%
Withdrawn from analysis				
Surgical intervention	1	0.9%	1	1.0%
Medical disqualification	4	3.7%	1	1.0%
Lost to follow-up	4	3.7%	0	0.0%
Total subjects	107	100.0%	99	100.0%

treatment by pulsed electromagnetic fields for pseudarthrosis perhaps is related to the limited ability for revascularization in this particular setting. This perhaps is related to the greater correlation of failure with the smoking population as well. Technical factors may be significant. In an earlier study, a higher success rate was noted when a double coil was used rather than a single coil. A single coil offered a success rate of 77% (10 of 13). The double coil offers a success of 92.2%. Apparently the double coil offers a slightly higher magnetic field (1.8 gauss compared with 4 gauss). Whether these factors are really significant, of course, would need further evaluation.

The use of the electromagnetic brace offers a small intrusion onto patient comfort. Certainly patient compliance is an important factor. Discomfort with the use of the brace is a realistic complaint, but improvement in brace design should resolve this. There are apparently no adverse affects of significance with the use of this treatment. Potential for benefit is demonstrated in a statistical manner. Thus it is reasonable to advocate its use for further application in fusion procedures.

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