The Effect of Pulsed Electromagnetic Fields in the Treatment of Osteoarthritis of the Knee and Cervical Spine. Report of Randomized, Double Blind, Placebo Controlled Trials

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ABSTRACT. ***Objective.*** We conducted a randomized, double blind clinical trial to determine the effectiveness of pulsed electromagnetic fields (PEMF) in the treatment of osteoarthritis (OA) of the knee and cervical spine.

Methods. A controlled trial of 18 half-hour active or placebo treatments was conducted in 86 patients with OA of the knee and 81 patients with OA of the cervical spine, in which pain was evaluated using a 10 cm visual analog scale, activities of daily living using a series of questions (answered by the patient as never, sometimes, most of the time, or always), pain on passive motion (recorded as none, slight, moderate, or severe), and joint tenderness (recorded using a modified Ritchie scale). Global evaluations of improvement were made by the patient and examining physician. Evaluations were made at baseline, midway, end of treatment, and one month after completion of treatment.

Results. Matched pair t tests showed extremely significant changes from baseline for the treated patients in both knee and cervical spine studies at the end of treatment and the one month followup observations, whereas the changes in the placebo patients showed lesser degrees of significance at the end of treatment, and had lost significance for most variables at the one month followup. Means of the treated group of patients with OA of the knee showed greater improvement from baseline values than the placebo group by the end of treatment and at the one month followup observation. Using the 2-tailed t test, at the end of treatment the differences in the means of the 2 groups reached statistical significance for pain, pain on motion, and both the patient overall assessment and the physician global assessment. The means of the treated patients with OA of the cervical spine showed greater improvement from baseline than the placebo group for most variables at the end of treatment and one month followup observations; these differences reached statistical significance at one or more observation points for pain, pain on motion, and tenderness.

Conclusion. PEMF has therapeutic benefit in painful OA of the knee or cervical spine. (*J Rheumatol 1994;***21:1903–11**)

Key Indexing Terms:
OSTEOARTHRITIS

PULSED MAGNETIC FIELDS

Pulsed electromagnetic fields (PEMF) have been used widely to treat nonhealing fractures and related problems in bone healing since approval by the Food and Drug Administration (FDA) in 1979, with a success rate averaging 70–80% in a wide variety of centers in several countries[1,2]. The original basis for the trial of this form of therapy was the observation that physical stress on bone causes the appearance of tiny electric currents (piezoelectric potentials) that are thought to be the mechanism of transduction of the physical stresses into a signal that promotes bone formation. Direct electric field stimulation was successful in treatment of nonunion[3], but problems with the invasive placement of electrodes led to the use of PEMF, with the expectation that these magnetic impulses would generate small induced currents (Faraday currents) in the highly conductive extracellular fluid, mimicking the piezoelectric potentials[1,2].

The piezoelectric potentials, originally thought to be due to phenomena occurring at the surface of crystals in the bone, have been shown to be due primarily to movement of fluid containing electrolytes in channels of the bone containing organic constituents with fixed charges, generating what are called "streaming potentials"[4]. Studies of electrical phenomena in cartilage have demonstrated a mechanical-electrical transduction mechanism that resembles those described in bone, appearing when cartilage is mechanically compressed, causing movement of fluid and electrolytes, leaving unneutralized negative charges in the proteoglycans and collagen in the cartilage matrix[5,6]. These streaming potentials apparently serve a purpose in cartilage similar to that in bone, transducing mechanical stress to an electrical (or electromagnetic) phenomenon capable of stimulating chondrocyte synthesis of matrix components[7-9].

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One of us (RM) developed a unique delivery system to apply PEMF *in vivo*. By means of an extensive trial involving about 1,000 patients in Europe, one constellation of variables was determined to be most effective in treating patients with arthritis and related sports-type injuries. These variables have been tested in the United States, and a preliminary report of the use of this device to treat osteoarthritis (OA) appeared in this journal[10]. Since that report, further randomized double blind placebo controlled trials of PEMF in the therapy of patients with OA have been conducted by us, and these trials are the subject of our report.

MATERIALS AND METHODS

Three treatment centers were established to conduct these double blind trials, in Waterbury, CT, Danbury, CT, and Melville, NY. Staff at each center were trained in the conduct of double blind trials. Rheumatologists and specially trained physicians' assistants obtained historical and subjective data and made all the observations. Rheumatologists were recruited from the communities with treatment centers; in some instances they followed their own patients; 57% of the patient examinations were done by one of us (DT); other rheumatologists did 5%; one physician's assistant did 29%, and another 10% of the examinations.

The treatment device has been described[10]. Briefly, it consisted of a magnetic field generator, an electronic interface, and a toroid coil. The coil used for the knee patients had an internal diameter of 11"; the coil for the cervical spine patients was 22" in diameter. Patients with knee disease sat in a chair with the coil positioned eccentrically over the involved knee. Patients with cervical spine involvement lay on a mattress in a specially designed polycarbonate half-shell device, with a movable coil on tracks that allowed it to be positioned over the neck area. The internal face of the coil remained up to 5" from the area under treatment, well within the magnetic field lines.

The device, called the M-T System, generated extremely low frequency (ELF) PEMF. It consisted of 3 integrated components, a magnetic field generator, an electronic interface, and a segmented single toroid coil with annular windings that produced pulsed DC elliptical magnetic fields. The system used a coil current of <2 A with 120 V. The following energy characteristics were applied stepwise to the area of the joint being treated: 5 Hz, 10–15 gauss for 10 min; 10 Hz, 15–25 gauss for 10 min, and 12 Hz, 15–25 gauss for 10 min. The waveform was quasirectangular with abruptly rising and deteriorating waveform; pulse burst duty cycle of up to 0.8. The number of pulses/burst is determined by the frequency; the maximum was 20. The same treatment protocol was used for both the patients with knee involvement and those with cervical spine involvement.

Patient selection. All patients with OA of the knee met the criteria published by Altman[11]. If radiographs taken in the previous 4 months were not available, new ones were obtained. Patients with knee disease were radiographed standing with body weight distributed as evenly as possible between the 2 legs. Radiographs of the knee films were analyzed using the criteria of Brandt, *et al*[12] without knowledge of the treatment status or the patient data obtained. No patient was included in the prior report[10].

Patients with cervical spine pain were admitted to the study if radiographs showed evidence of disk space narrowing with osteophyte formation and/or subchondral sclerosis in one or more locations; osteophyte formation and subchondral sclerosis of facet joints were also accepted as evidence of OA.

Entry criteria. The patients were required to be at least 35 years of age, with local symptoms such as pain and stiffness of at least one-year duration, persistent despite conventional treatment. Patients were instructed not to change their basic therapeutic regimen, including drugs and physical therapy, during the period of treatment and observation. The use of medications was checked by history at each evaluation point, but no pill counts were done. Informed consent for entry into a double blind trial was obtained.

Exclusions. Patients who had changed their therapeutic regimen within one month before evaluation were excluded, including any who had changed their dose of nonsteroidal antiinflammatory drugs (NSAID) during that period. Women who could be pregnant were also excluded; women of childbearing age were required to agree to use contraception. Other exclusions included the presence of an unstable medical illness or a cardiac pacemaker.

Method of randomization. When patients satisfied entry criteria, a central office was called. One research associate kept the list of 1,000 random numbers, divided into pairs, the higher of which was to receive treatment and the lower placebo. When called, the research associate assigned the value for the next number to that patient. Separate lists of random numbers were kept for the patients with knee involvement and those with cervical spine involvement, resulting in separate randomization by site of involvement.

Only the therapy technician at the treatment center was informed, by means of a code, of the treatment status of an individual patient. The therapy apparatus has a set of light emitting diodes that pulse to signal that the coil is being energized; these were covered and not visible to patients in the double blind trials, so that neither the patient in the trial nor any other patient in the center, nor any other staff could tell which patients were receiving active treatment. A mechanical timing device was activated for the 30 min period of treatment for each patient. The M-T System does not generate any noise, and there is no thermal effect or other sensation while treatment is being received; it thus aids in the maintenance of the double blind nature of the trial.

After receiving all 18 treatments and the evaluation at the followup one month later, the patient was informed whether treatment actually had been administered. If the patient had received placebo, active treatment was offered.

Treatment. The knee was placed in the coil with the most painful site positioned eccentrically against the z axis (inside of the coil), resting on a pillow in a comfortable position. Patients treated for cervical spine disease were recumbent, with the back of the neck against the coil, resting on a pillow. Treatments were given for 30-min periods, 3 to 5 times a week, for 18 treatments.

Observations. The case report form used for every patient included record of biographic and basic clinical data, pertinent history, and baseline medications. Laboratory tests and, if necessary, radiographs were obtained before treatment was begun. Laboratory tests included hematocrit, white blood cell counts, serum electrolytes, creatinine, and erythrocyte sedimentation rate, alkaline phosphatase, AST, as well as urinalysis. These tests were repeated at the end of the period of treatment.

Evaluations were made at baseline, about the midpoint of therapy, at the time of the last (18th) treatment, and one month later. At each evaluation point, the patient was asked to mark the degree of pain in the affected site during the past week, using a 10-cm visual analog scale (VAS).

A series of questions concerning activities of daily living (ADL) were asked; for each question, the patient was asked: How often do you have [e.g., right knee] pain or difficulty with [nature of activity]: never, sometimes, most of the time or always. For patients with OA of the knee, inquiry was made about the following specific activities: standing for >15 min, walking $>$ one block, climbing up or down a flight of stairs, getting up from a chair or toilet, turning in bed at night, dressing (i.e., putting on shoes or socks), kneeling or reaching into a low cabinet. For patients with cervical spine disease, the following activities were questioned: How often do you have pain or difficulty with getting out of bed in the morning, picking up clothing from the floor, getting out of a car, performing housework, cooking or cleaning, sitting for 2 h in a restaurant or while watching TV, or prolonged standing or walking, such as shopping? For scoring, never was graded as 0, sometimes as 1, most of the time as 2, and always as 3.

In both instances, there were 7 activities questioned, and the score for pain at night was added to this value; the total score for ADL could thus range from 0 to 24.

The physician recorded the degree of pain on motion (none, slight, moderate, or severe) and tenderness, using the Ritchie scale as described for patients with OA by Doyle, *et al*[13]. For both of these observations, the score for none was assigned as 0, slight as 1, moderate as 2, and severe as 3. Any soft tissue swelling or synovial effusion was noted, but this finding was rare and the data were not analyzed.

At each of the evaluations after the baseline, the patient was asked to quantitate any improvement by marking a 10 cm VAS.

At the end of treatment and the one month followup evaluation, the observing physician was asked to record a global assessment of overall improvement, using a 4-point scale (0 = none, 1 = slight, 2 = good, and 3 = excellent).

Statistical methods. Data were analyzed for change from baseline for each observation and for the degree of improvement reported by the patient or the physician (global assessment) comparing the means of the treated and placebo groups. The baseline data were plotted for the frequency distribution at each point of severity and showed a reasonably good Gaussian distribution for all of the variables followed. Therefore, the unpaired 2-tailed Student's t test was used for determination of p values for pain and ADL difficulty. Nonparametric t tests (Cochran-Mantel-Haenszel analysis) were used for categorical data (pain on passive motion, tenderness, and physician global assessment); these are the values reported in Tables 2–4, but the results were essentially the same as parametric t tests for these observations. Analysis of covariance was done to determine if there was an effect of severity of baseline pain or ADL on improvement at subsequent visits. Two-tailed χ^2 test (Fisher's exact test) was used to compare the results for numbers of cases with specific levels of improvement (Table 6).

The data from the 2 trials were combined in a meta-analysis, since the criteria and methods were the same in the 2 trials; only the nature of the questions in the ADL assay were different. The combined data are given in Table 6.

RESULTS

Table 1 gives the characteristics of the 2 groups of patients at baseline for average age, duration of symptoms, radiographic grade of severity of the knee OA, weight, use of NSAID, and other characteristics. The treated and placebo groups generally were similar in regard to these characteristics.

Table 1. *Characteristics of treated and placebo groups of patients. Figures are means ± SD*

	Patients with Knee OA	
	Treated (n = 42)	Placebo (n = 44)
Sex	29F/13M	31F/13M
Age	69.24 ± 11.48	65.82 ± 11.66
Weight (lb)	178.02 ± 46.03	171.82 ± 39.96
Duration of symptoms (yr)	9.08 ± 8.85	7.36 ± 7.15
Average radiographic grade	2.86 ± 0.87 (n = 28)	2.57 ± 1.13 (n = 37)
Use of NSAID	18	16
Use of other drugs	28	37
	Patients with OA of the Cervical Spine	
	Treated (N = 42)	Placebo (N = 39)
Sex	12M/30F	12M/26F
Age	61.24 ± 13.40	67.38 ± 8.02
Weight (lb)	161.2 ± 39.0	161.8 ± 31.8
Duration of symptoms (yr)	7.43 ± 6.66	8.07 ± 8.01
Use of NSAID	21	7
Use of other drugs*	26	31

* Other drugs were almost entirely antihypertensives, antianginal agents and other drugs for cardiac disease.

The baseline data (Table 2) show that the treated patient started out with slightly worse findings than the placebo patients in regard to several variables; among the cervical spine patients, the difference for total pain and pain on passive motion was statistically significant.

Matched pair analyses of the followup observations on each patient are shown in Table 3. Improvement in pain score for the patients with knee OA was statistically significant for the treated patients at each observation; for the placebo patients, less significant p values were found, and by the one month followup point, significance was lost. Improvement in ADL was statistically significant for both groups at each observation point, but considerably more significant p values were found for the treated patients. Change in the pain on motion scores was significant for the treated patients at the end of treatment and one month followup points but only at the end of treatment for the placebo patients. Change in tenderness scores also showed statistical significance for the treated patients but much less significance for the placebo patients, and no significance at the one month followup point.

The data for the patients with cervical spine involvement showed a similar pattern, with the changes from baseline in the treated patients always showing greater statistical significance by the end of treatment and at followup.

The efficacy of the treatment also was evaluated comparing the means of the treated group of patients to those of the placebo patients for the change from baseline findings for each variable at each observation point. The observations made on the patients with knee OA are shown in Table 4 and those for patients with OA of the cervical spine are shown in Table 5. A meta-analysis of the combined data for the observations made in the same fashion in the 2 groups of patients are presented in Table 6.

By the end of treatment, the mean values for the change from baseline for the treated patients was always higher (showed greater improvement) than the means of the placebo

Table 2. *Baseline findings of treated and placebo patients. Figures are means ± SD*

	Patients with Knee OA		
	Treated (N = 42)	Placebo (N = 44)	
Pain (mm)	70.74 ± 22.50	63.59 ± 21.01	
ADL difficulty	15.39 ± 4.70	14.48 ± 4.07	
Pain on motion	1.63 ± 0.79	1.60 ± 0.82	
Tenderness	1.93 ± 0.95	2.01 ± 0.93	
	Patients with OA of the Cervical Spine		
	Treated (N=42)	Placebo (N=39)	p Value
Pain (mm)	72.02 ± 18.45	62.3 ± 24.16	0.045
ADL difficulty	11.94 ± 5.63	11.5 ± 5.27	NS
Pain on motion	2.20 ± 0.58	1.87 ± 0.65	0.018
Joint tenderness	2.01 ± 0.69	1.73 ± 0.81	0.097

Table 3. *p Values for matched pair t tests of data for treated and placebo patients, comparing baseline values to later observations*

Efficacy Variable		Comparison of Baseline Values to Midway	End of Treatment	1 Mo. Followup
		Patients with Knee OA		
Pain	Treated	<0.0001	<0.0001	0.001
	Placebo	0.0006	0.02	0.07
ADL	Treated	0.0008	<0.0001	0.0003
	Placebo	0.03	0.005	<0.01
Pain on motion	Treated	0.07	0.0003	<0.0001
	Placebo	0.2	0.009	0.2
Tenderness	Treated	0.0008	<0.0001	0.0003
	Placebo	0.02	0.02	0.2
		Patients with OA of the Cervical Spine		
Pain	Treated	<0.0001	<0.0001	<0.0001
	Placebo	0.03	0.0002	0.009
ADL	Treated	0.0006	0.0009	0.003
	Placebo	0.008	0.002	0.04
Pain on motion	Treated	0.005	<0.0001	<0.0001
	Placebo	0.3	0.02	0.6
Tenderness	Treated	0.0001	<0.0001	<0.0001
	Placebo	0.005	0.002	0.1
Limitation of flexion/extension				
	Treated	0.07	0.001	0.0002
	Placebo	0.4	0.3	0.6
Limitation of rotation	Treated	0.04	<0.0001	<0.0002
	Placebo	0.003	0.004	0.02

group. The differences between the means was greater at the end of treatment than at the midway observation, primarily because of much greater improvement in the treated group. The differences between the means increased further between end of treatment and the one month followup observation point for several of the observations, primarily because of a greater decline in the mean of the placebo group.

The differences in the means of the change from baseline for the pain score was significantly greater at all 3 observation points. Most of the other variables showed statistically significant differences at one or more time points. The exception was the patient assessment of overall improvement; the differences in the means were not great enough for statistical significance given the standard deviations.

The changes from baseline values were analyzed for degree of improvement, expressed as change divided by the baseline value (percentage of improvement). The treated patients with knee OA averaged between 29 and 36% improvement in each of the variables followed at the end of treatment, while the placebo group averaged between 11 and 19% improvement. At the one month followup period, average improvement ranged between 21 and 31% in the treated group and −0.3% to + 16% in the placebo group.

The treated cases of OA of the cervical spine averaged between 30 and 35% improvement at the end of treatment and 20 to 39% at the one month followup point, while the placebo patients in this portion of the trial averaged 17 to 27% improvement at the end of treatment and 0 to 18% change at the one month followup.

The degree of improvement at the last followup observation in each patient was assessed by determining how many of the observations of each patient showed ≥25% improvement, or ≥25 mm improvement in the VAS checked by the patients for overall improvement, or a physician global assessment of improvement >1. Thus, there were 6 items analyzed for these criteria for clinically valuable improvement. These data are shown in Tables 5A and B; significant p values were found for differences in the number of items showing improvement; for example, improvement in ≥3 variables was considered clinically meaningful and was found in 57 (69.5%) of the treated patients and 37 (45.1%) of the placebo patients. Despite the strong placebo effect, these data had a χ^2 p value of 0.003. Conversely, analysis of the numbers of patients who failed to show this degree of improvement in any category (Table 5B) revealed 5 (6.1%) in the treated group and 22 (26.8%) in the placebo group (p value 0.0006).

Several additional statistical analyses of the results for the patients with OA of the knee and OA of the cervical spine were done separately and together. Analysis of the data for study site interactions revealed that the effect of treatment was consistent across centers, and that the centers are statistically "poolable"; no statistical interactions were found that would preclude pooling of the data from the 2 trials. Analysis of

Table 4. *Observations for patients with knee OA at each time period for each variable followed. Figures are means ± SD. p Values are given at or near significance (≤ 0.1)*

Efficacy Variable	Time of Observation	Changes from Baseline Value		
		Treated (N)	Placebo (N)	p Value
Pain	Midway	21.10 (42) ± 28.92	14.61 (44) ± 21.39	NS
	End of treatment	26.55 (40) ± 33.29	11.98 (44) ± 30.79	0.04
	One month followup	23.65 (37) ± 36.07	9.56 (39) ± 33.65	0.08
ADL difficulty	Midway	3.54 (42) ± 4.56	2.08 (44) ± 7.76	NS
	End of treatment	5.38 (40) ± 5.17	2.87 (41) ± 5.90	0.04
	One month followup	4.81 (37) ± 6.14	3.05 (39) ± 6.12	NS
Pain on passive motion	Midway	0.23 (42) ± 0.72	0.26 (41) ± 0.90	NS
	End of treatment	0.61 (40) ± 0.91	0.41 (41) ± 0.93	NS
	One month followup	0.60 (34) ± 0.81	0.19 (38) ± 0.91	0.07
Tenderness	Midway	0.46 (42) ± 0.80	0.34 (40) ± 0.65	NS
	End of treatment	0.76 (40) ± 0.89	0.37 (41) ± 0.90	0.05
	One month followup	0.62 (34) ± 0.87	0.17 (38) ± 0.85	0.03
		Overall Assessment Variables		
Patient's overall assessment	Midway	33.64 (42) ± 29.95	28.11 (44) ± 6.25	NS
	End of treatment	51.09 (40) ± 32.30	34.15 (41) ± 30.90	0.02
	One month followup	40.85 (34) ± 35.49	34.36 (39) ± 33.10	NS
Physician global assessment	End of treatment	1.74 (40) ± 0.90	1.29 (41) ± 1.04	0.04
	One month followup	1.63 (34) + 1.05	1.22 (39) ± 1.10	0.1

the results based on baseline severity of pain and ADL by analysis of covariance revealed that severity was significantly associated with the degree of improvement recorded at each visit, but tests of treatment by baseline interaction showed no significant departure from parallelism of regression lines in the 2 groups of patients. Tests of treatment effect were not changed to an important degree by inclusion of baseline as a covariate.

Side effects. No untoward effects, symptoms, clinical findings, or laboratory observations were observed in any patient treated in our study.

Withdrawals. Eleven patients withdrew from the double blind trial of knee OA and 8 patients from the trial of OA of the cervical spine before completing treatment, for the reasons listed below; in each instance the decision to withdraw was made before the code was broken for that patient. The decision to use all valid observations obtained for patients who were absent from one of the scheduled exams was made before the study was instituted.

Eight patients randomized to treatment withdrew from the study of knee OA before the midway evaluation because of compliance or transportation difficulties. Data from these patients were not included in analysis of patient characteristics or baseline observations. Two patients were excluded from the study after receiving randomization numbers because the diagnosis was found to be erroneous; no data on these patients were included in the analysis. One patient voluntarily discontinued treatment after midway because of inability to keep appointments because of a work schedule conflict. Available data (baseline and midway) were included.

There were 8 withdrawals from the study of OA of the cervical spine; all occurred before the code was broken and any data analyzed. One patient could not lie still for the 30 min treatments; one became worse after 11 treatments and

Table 5. *Observations for patients with OA of the cervical spine at each time period for each variable followed. Figures are mean ± SD. p Values are given that are at or near significance (≤ 0.1)*

Efficacy Variable	Time of Observation	Change from Baseline Value Treated (N)	Placebo (N)	p Value
Pain	Midway	22.43 (42) ± 27.21	12.03 (39) ±29.72	0.1
	End of treatment	27.85 (41) ±27.34	16.31 (39) ±24.28	0.040
	One month followup	25.87 (38) ± 30.22	14.66 (32) ±29.39	0.1
ADL difficulty	Midway	3.01 (42) ± 4.94	2.31 (39) ± 4.77	NS
	End of treatment	3.79 (41) ± 6.70	3.10 (39) ± 5.80	NS
	One month followup	3.78 (38) ± 7.35	2.14 (32) ± 5.57	NS
Pain on passive motion				
	Midway	0.43 (42) ± 0.73	0.18 (39) ± 1.00	NS
	End of treatment	0.79 (41) ± 0.80	0.38 (39) ± 0.97	0.03
	One month followup	0.95 (38) ± 0.92	0.13 (32) ± 0.90	0.0004
Tenderness	Midway	0.55 (42) ± 0.78	0.47 (39) ± 0.94	NS
	End of treatment	0.78 (41) ± 1.04	0.62 (39) ± 1.13	NS
	One month followup	0.83 (38) ± 1.05	0.25 (32) ± 0.92	0.02
		Global Assessment Variables		
Patients' assessment of improvement				
	Midway	29.81 (42) ± 27.97	30.77 (39) ± 25.90	NS
	End of treatment	42.71 (41) ± 35.55	46.18 (39) ± 31.71	NS
	One month followup	41.18 (38) ± 35.88	40.00 (32) ± 32.27	NS
Physician global assessment				
	End of treatment	1.59 (41) ± 1.05	1.47 (39) ± 0.95	NS
	One month followup	1.51 (38) ± 1.02	1.23 (32) ± 1.00	NS

refused further treatment (it was later found that she was receiving placebo treatments), 4 withdrew because of transportation or scheduling difficulties, one because she wanted to wait for FDA approval of this form of treatment, and one because the diagnosis was determined to be in error after radiographs were reviewed.

Several patients in both groups were seen at baseline, midway, and end of treatment, but failed to appear for one month followup. All data on these patients, up to and including the last observation point, were included for analysis.

No treated patient dropped out of either study because of worsening of symptoms or development of side effects.

DISCUSSION

Although clinical studies of the efficacy of treatment of OA are clearly based on subjective phenomena, the use of VAS and consistent patterns of evaluation have provided reasonably satisfactory data for evaluating effectiveness of therapy in this disease. Our observations are similar to those that have been tested in other studies, particularly the use of VAS for assessment of severity of pain[14]. The use of a randomized, double blind trial design also strengthens the interpretability of the data. There was a strong placebo effect, as is usually seen with new forms of therapy in all types of arthritis and considerable variability from patient to patient, but a greater degree of improvement was found consistently in the treated

Table 6. *Meta-analysis of double blind trials of PEMF in treatment of knee and cervical spine OA: Data for observations conducted in the same fashion are combined. Data given means and ± SD for changes from baseline at each observation point. p Values are at or near significance (≤ 0.1)*

Efficacy Variable	Time of Observation	Change from Baseline		p Value
		Treated (N)	Placebo (N)	
Pain	Midway	21.76 (84) ± 28.08	13.38 (83) ± 27.18	0.052
	End of treatment	27.21 (81) ± 30.43	14.03 (79) ± 28.06	0.005
	One month followup	24.77 (75) ± 33.26	11.86 (71) ± 31.90	0.018
ADL difficulty	Midway	3.27 (84) ± 4.76	2.17 (83) ± 4.79	0.139
	End of treatment	4.57 (81) ± 6.05	2.98 (79) ± 5.89	0.094
	One month followup	4.29 (75) ± 6.80	2.64 (71) ± 5.90	0.120
Pain on passive motion				
	Midway	0.33 (84) ± 0.73	0.20 (83) ± 0.94	0.319
	End of treatment	0.70 (81) ± 0.86	0.41 (79) ± 0.95	0.045
	One month followup	0.78 (72) ± 0.089	0.16 (70) ± 0.91	< 0.0001
Joint tenderness	Midway	0.51 (84) ± 0.79	0.37 (83) ± 0.82	0.263
	End of treatment	0.77 (81) ± 0.97	0.48 (79) ± 1.03	0.069
	One month followup	0.73 (72) ± 0.98	0.21 (70) ± 0.88	0.001

group of patients by the end of treatment and at the followup examination one month later.

Recent reports of clinical studies of the effect of NSAID on various variables in patients with knee OA can serve as a basis for comparison of the results of PEMF with those of NSAID. For example, Bradley and Brandt, *et al*[15] studied the effectiveness of acetaminophen and 2 doses of ibuprofen on pain and disability, using a Health Assessment Questionnaire. With acetaminophen, pain improved by an average of 22.6% and disability by 9.3%. Ibuprofen, 1200 mg/day resulted in an improvement in the pain score of 20.0% and disability by 8.8%, while 2400 mg/day gave a 21.7% improvement in pain and 12.9% improvement in disability score.

Bellamy, *et al*[16] using VAS similar to those used in our study (the WOMAC Osteoarthritis Index), compared the effectiveness of tenoxicam and diclofenac in the therapy of knee OA. At the end of 4 weeks, the pain score had decreased by 22.2% with tenoxicam and 36.9% with diclofenac. The scale for physical function improved by 26.6% with tenoxicam and 25.8% with diclofenac.

Our studies of the use of PEMF in the treated patients with knee OA show that at the end of treatment pain had improved by an average of 37.3% and ADL by 35.0%. In the studies of NSAID, effects last only as long as administration of the drug is continued, hence our comparison was made to results at the end of therapy in our study; however, it is worth noting that the effect of therapy was still notable in patients one month after completion of therapy. Studies of the duration of this effect are in progress.

It is worth noting that for the purpose of the study, the experimental treatment was given without changing any other aspect of the patients' regimen; muscle atrophy and disease in other joints were not affected by the treatment. We feel that this accounted for the fact that patients consistently reported less overall improvement than improvement in pain in the treated joint.

Many hypotheses have been developed to explain the action of PEMF on tissues, and numerous observations have been made of *in vitro* as well as experimental *in vivo* effects in laboratory situations, including specific effects on cartilage. For example, electric stimuli and PEMF enhanced cartilage repair processes; external oscillating electric fields augmented incorporation of ^{3}H-thymidine into DNA of chondrocytes isolated from embryonic chick epiphyses[17], and capacitively coupled electric fields stimulated cell proliferation (^{3}H-thymidine incorporation) and glycosaminoglycan (GAG) synthesis ($^{35}SO_4$ uptake) by isolated bovine growth plate chondrocytes[18]. Pulsating direct current also was reported to augment the repair of induced osteochondral defects in rabbit femoral condyles[19]. Recently, a device generating pulsed direct currents applied to the knee

was reported to have beneficial effects in patients with OA of that joint[20].

In laboratory studies with PEMF, chondrocytes from rabbit articular cartilage showed enhanced ^{35}S-sulfate incorporation into proteoglycan, which was the same molecular size and aggregability as controls[21]. PEMF also were shown to increase ^{35}S and ^{3}H-thymidine incorporation into cultured bovine chondrocytes[22]. Chick tendon fibroblasts showed increased collagen synthesis when stimulated by PEMF, without any change in collagen phenotype[23].

PEMF can alter metabolism of osteocytes *in vitro*, including causing an increase in intracellular alkaline phosphatase in tissue culture. Currents induced by PEMF occur primarily in the periphery of a conducting medium, while magnetic energy would penetrate uniformly. To determine if the effect of PEMF was due to induced currents or a direct effect of the magnetic energy on the cells, McLeod, *et al*[24] stained cultured osteocytes for alkaline phosphatase after exposure to PEMF; the increase in the enzyme was found in the cells in the periphery of the culture, supporting the conclusion that the effect was mediated by induced currents.

One mechanism suggested for the actions of these electric and magnetic stimuli is an effect on charged transmembrane molecules, such as receptors. For example alteration in chondrocyte receptor activation by parathyroid hormone and transforming growth factor ß by PEMF has been demonstrated[25]. Altered receptor activity is thought to underlie the observation that PEMF had a synergistic effect on proteoglycan synthesis by bovine articular chondrocytes when combined with epidermal growth factor or fibroblast growth factor[25].

Observations have also been made of the effects of these low frequency, nonionizing forms of radiation on a variety of other tissues[26]; PEMF cause movement of calcium and other ions across cell membranes and stimulate DNA transcription with increased protein synthesis[27-29].

Despite the extensive studies of the effects of PEMF in numerous laboratories and the demonstration of a variety of *in vitro* effects that could be relevant to cartilage repair, such as increased proteoglycan and collagen synthesis by chondrocyte cultures, the actual mechanism of action underlying the clinical effects observed in the studies reported above are not known. In these clinical studies, no evidence for a general analgesic effect was observed, although nervous system effects of PEMF are known, and this possibility has not been rigorously excluded. Despite the lack of knowledge of the mechanism of action, some speculation regarding possibilities is warranted.

Discussion of relief of pain in OA introduces the subject of the complexity and variability of the mechanisms responsible for the pain in this disease. The role of cartilage breakdown in the pathogenesis of the disease process is well established, as is the role of the clustered fixed negative charges in the GAG in cartilage in absorbing compressive stresses. In the development of OA, the concentration of the GAG is decreased; therefore, the ability of cartilage to absorb compressive stresses is impaired and more pressure is thus transmitted to the underlying bone where pain receptors are present (especially in the periosteum). If a form of therapy results in increased GAG concentration in the articular cartilage, it would enhance the ability of that tissue to absorb compressive stresses, decreasing the transmission of such stresses to the underlying bone. Such a phenomenon might underly the beneficial effects of this form of therapy, as well the clinical improvement expected following the administration of agents being developed, which decrease the rate of loss of GAG from cartilage ("chondroprotective" agents).

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REFERENCES

1. Bassett CAL, Pilla AA, Pawluk RJ: A non-operative salvage of surgically resistant pseudarthrosis and non-unions by pulsing electromagnetic fields. A preliminary report. *Clin Orthop 1977;*124:128–43.
2. Bassett CAL, Mitchell SN, Gaston SR: Pulsing electromagnetic field treatment in ununited fractures and failed arthrodeses. *JAMA 1982;*247:623–8.
3. Brighton CT, Pollack SR: Treatment of recalcitrant non-union with a capacitively coupled electrical field. A preliminary report. *J Bone Joint Surg 1985;*67A:577–85.
4. Guzelsu N, Walsh WR: Streaming potential in intact wet bone. *J Biomech 1990;*23:673–85.
5. Frank EH, Grodzinsky AJ: Cartilage electromechanics. I. Electrokinetic transduction and the effects of electrolyte pH and ionic strength. *J Biomech 1987;*20:615–27.
6. Frank EH, Grodzinsky AJ: Cartilage electromechanics. II. A continuum model of cartilage electrokinetics and correlation with experiments. *J Biomech 1987;*20:629–39.
7. Parkkinen JJ, Mikko JL, Helminen HJ, Tammi M: Local stimulation of proteoglycan synthesis in articular cartilage explants by dynamic compression *in vitro*. *J Orthop Res 1982;*10:610–20.
8. Sah RLY, Kim Y, Doong JH, Grodzinsky AJ, Plass AHK, Sandy JD: Biosynthetic response of cartilage explants to dynamic compression. *J Orthop Res 1989;*7:619–36.
9. Sah RLY, Grodzinsky AJ, Plaas AHK, Sandy JD: Effects of static and dynamic compression on matrix metabolism in cartilage explants. In: Kuettner KE, Schleyerbach R, Peyron JG, Hascall VC, eds. *Articular Cartilage and Osteoarthritis.* New York: Raven Press, 1992:373–92.
10. Trock DH, Bollet AJ, Dyer RH Jr, Fielding LP, Miner WK, Markoll R: A double blind trial of the clinical effects of pulsed electromagnetic fields in osteoarthritis. *J Rheumatol 1993;*20:456–60.

11. Altman RD: Classification of diseases: Osteoarthritis. *Semin Arthritis Rheum 1991;*(suppl 2)20:40–7.
12. Brandt KD, Fife RS, Braunstein EM, Katz B: Radiographic grading of the severity of knee osteoarthritis: relation of the Kellgren and Lawrence grade to a grade based on joint space narrowing, and correlation with arthroscopic evidence of articular cartilage degeneration. *Arthritis Rheum 1991;*34:1381–6.
13. Doyle DV, Dieppe PA, Scott J, Huskisson EC: An articular index for the assessment of osteoarthritis. *Ann Rheum Dis 1981;*40:75–8.
14. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt L: Validation study of WOMAC: a health status instrument for measuring clinically-important patient-relevant outcomes following total hip or knee arthroplasty in osteoarthritis. *J Orthop Rheum 1988;*1:95–108.
15. Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI: Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. *N Engl J Med 1991;*325:87–91.
16. Bellamy N, Buchanan WW, Chalmers A, *et al:* A multicenter study of tenoxicam and diclofenac in patients with osteoarthritis of the knee. *J Rheumatol 1993;*20:999–1004.
17. Rodan GA, Bourret LA, Norton LA: DNA synthesis in cartilage cells is stimulated by oscillating electric fields. *Science 1978;*199:690–2.
18. Armstrong PF, Brighton CT, Star AM: Capacitively coupled electrical stimulation of bovine growth plate chondrocytes grown in pellet form. *J Orthop Res 1988;*6:265–71.
19. Lippiello L, Chakkalakal D, Connelly JF: Pulsing direct current-induced repair of articular cartilage in rabbit osteochondral defects. *J Orthop Res 1990;*8:266–75.
20. Zizic TM, Hoffman KC, Holt PA, Hungerford DS, O'Dell JR, Jacobs M, *et al:* Treatment of osteoarthritis of the knee with pulsed electrical stimulation (abstr). *Arthritis Rheum 1993;*(suppl)36:S167.
21. Aaron RK, Plass AHK: Stimulation of proteoglycan synthesis in articular chondrocyte cultures by a pulsed electromagnetic field. *Trans Orthop Res Soc 1987;*12:273.
22. Grande DA, Magee FP, Weinstein AM, McLeod BR: The effect of low-energy combined AC and DC magnetic fields on articular cartilage metabolism. *Ann NY Acad Sci 1991;*635:404–7.
23. Murray JC, Farndale RW: Modulation of collagen in cultured fibroblasts by a low-frequency, pulsed magnetic field. *Biochimica et Biophysica Acta 1985;*838:98–105.
24. McLeod KJ, Guilak F: Differential effects of normal and tangential ELF electric field exposure on bone cells (ROS 17/2.8) growing in monolayer (abstr). In: *BEMS Abstract Book Fifteenth Annual Meeting.* Los Angeles: The Bioelectromagnetics Society, 1993:99–100.
25. Aaron RK, Ciombor DM: Synergistic effects of growth factors and pulsed fields on proteoglycan synthesis in articular cartilage. *J Orthop Res 1992;*17:527.
26. O'Conner ME, Bentall RHC, Monahan JC, eds: *Emerging Electromagnetic Medicine.* Berlin: Springer-Verlag, 1990.
27. Liboff AR: Cyclotron resonance in membrane transport. In: Chiabrera A, Nicolini C, Schwan HP, eds. *Interactions Between Electromagnetic Fields and Cells. NATO ASI series. Series A, Life Sciences,* Vol 97. New York: Plenum Press, 1985:281–96.
28. Goodman R, Wei L, Xu J, Henderson A: Exposure of human cells to low-frequency electromagnetic fields results in quantitative changes in transcripts. *Biochim Biophys Acta 1989;*1009:216–20.
29. Goodman R, Weisbrot D, Uluc A, Henderson A: Transcription in *Drosophila melanogaster* salivary gland cells is altered following exposure to low-frequency electromagnetic fields: analysis of chromosome 3R. *Bioelectromagnetics 1992;*13:111–8.