Two Configurations of Static Magnetic Fields for Treating Rheumatoid Arthritis of the Knee: A Double-Blind Clinical Trial

Neil A. Segal, MD, Yoshitaka Toda, MD, Joseph Huston, MD, Yukihiko Saeki, MD, Masatoshi Shimizu, MD, Howard Fuchs, MD, Yasunori Shimaoka, MD, PhD, Robert Holcomb, MD, PhD, Michael J. McLean, MD, PhD

ABSTRACT. Segal NA, Toda Y, Huston J, Saeki Y, Shimizu M, Fuchs H, Shimaoka Y, Holcomb R, McLean MJ. Two configurations of static magnetic fields for treating rheumatoid arthritis of the knee: a double-blind clinical trial. Arch Phys Med Rehabil 2001;82:1453-60.

Objective: To assess the efficacy of a nonpharmacologic, noninvasive static magnetic device as adjunctive therapy for knee pain in patients with rheumatoid arthritis (RA).

Design: Randomized, double-blind, controlled, multisite clinical trial.

Setting: An American and a Japanese academic medical center as well as 4 community rheumatology and orthopedics practices.

Patients: Cohort of 64 patients over age 18 years with rheumatoid arthritis and persistent knee pain, rated greater than 40/100mm, despite appropriate use of medications.

Intervention: Four blinded MagnaBloc™ (with 4 steep field gradients) or control devices (with 1 steep field gradient) were taped to a knee of each subject for 1 week.

Main Outcome Measures: The American College of Rheumatology recommended core set of disease activity measures for RA clinical trials and subjects' assessment of treatment outcome.

Results: Subjects randomly assigned to the MagnaBloc (n = 38) and control treatment groups (n = 26) reported baseline pain levels of 63/100mm and 61/100mm, respectively. A greater reduction in reported pain in the MagnaBloc group was sustained through the 1-week follow-up (40.4% vs 25.9%) and corroborated by twice daily pain diary results ($p < .0001$ for each vs baseline). However, comparison between the 2 groups demonstrated a statistically insignificant difference ($p < .23$). Subjects in the MagnaBloc group reported an average decrease in their global assessment of disease activity of 33% over 1 week, as compared with a 2% decline in the control group ($p < .01$). After 1 week, 68% of the MagnaBloc treatment group reported feeling better or much better, compared with 27% of the control group, and 29% and 65%, respectively, reported feeling the same as before treatment ($p < .01$).

Conclusions: Both devices demonstrated statistically significant pain reduction in comparison to baseline, with concordance across multiple indices. However, a significant difference was not observed between the 2 treatment groups ($p < .23$). In future studies, the MagnaBloc treatment should be compared with a nonmagnetic placebo treatment to characterize further its therapeutic potential for treating RA. This study did elucidate methods for conducting clinical trials with magnetic devices.

Key Words: Arthritis, rheumatoid; Knee; Magnet; Rehabilitation.

RHEUMATOID ARTHRITIS (RA) is a disabling disease that limits patients' mobility, hampers work, and reduces patients' quality of life. Joint pain and inflammation, as well as patients' and physicians' assessment of disease activity and physical functioning, are used as indices of the effectiveness of treatments. Pharmacologic agents commonly used in the treatment of RA are often costly, and possess numerous potentially toxic side effects that limit their use with many patients. In older patients, chronic use of nonsteroidal anti-inflammatory drugs is associated with a high frequency of adverse effects.[1,2] Treatment with corticosteroids, other immunosuppressants, or disease-modifying anti-rheumatic drugs may result in harmful metabolic, renal, or pulmonary side effects, necessitating expensive laboratory monitoring. Minimizing toxic side effects and treatment costs is as important as therapeutic efficacy in identifying useful new treatment modalities.

Electromagnetic fields have been used therapeutically for 2000 years for a wide range of indications.[3] Placebo-controlled trials with pulsed electromagnetic field therapy have shown decreased pain and improved functional performance in patients with osteoarthritis of the knee.[4] There have also been reports of the use of static magnetic fields in treating fibromyalgia,[5] postoperative and traumatic wound pain, and ligamentous injuries,[6] but such studies cannot generally be found in the peer-reviewed medical literature. There have also been some placebo-controlled studies that demonstrated no significant relief of exercise-induced muscle pain[7] or low back pain (LBP).[8] The magnetic fields produced by the devices used in these studies had a tissue penetration of 1 to 3mm, which may not have been sufficient to have effected pain generators.

In contrast, pilot studies have suggested that certain static magnetic fields, with deeper tissue penetration, may be efficacious in the treatment of localized pain in postpoliomyelitis syndrome,[9] diabetic neuropathic leg pain,[10] chronic mechanical LBP[11] (also, Holcomb et al, unpublished data) and mechanical knee pain, as well as pain secondary to RA of the knee.[12] There is also evidence that inflammatory synovitis, induced in the hind joints of rats, can be significantly suppressed by exposure

From Vanderbilt University Medical School (Segal); Division of Rheumatology (Huston, Fuchs) and Department of Neurology (Holcomb, McLean), Vanderbilt University Medical Center, Nashville, TN; Orthopedics and Rheumatology Clinic (Toda); Department of Medicine III, Osaka University Medical Center (Saeki); Hino Hospital (Shimizu); and Yukioka Hospital (Shimaoka), Osaka Prefecture, Japan.

Accepted in revised form September 7, 2000.

Supported by the Vanderbilt University Medical Scholars Program and the Holcomb Medical Research Institute.

An organization with which one or more of the authors is associated has received or will receive financial benefits from a commercial party having a direct financial interest in the results of the research supporting this article.

Reprint requests to Michael J. McLean, MD, PhD, 437 MCS Vanderbilt University Medical Center, Nashville, TN 37232, e-mail: *michael.mclean@mcmail.vanderbilt.edu.*

0003-9993/01/8210-6335$35.00/0

doi:10.1053/apmr.2001.24309

to a static magnetic field.[13] With increasing evidence that both symptomatic pain and the pathologic cellular immune response in arthritic joints can be significantly suppressed with the use of static magnetic fields, larger randomized, double-blind, controlled clinical trials to assess the therapeutic efficacy of static magnetic fields are needed. Such trials will help in accurately assessing the effect of magnetic field therapy, which differs from pharmaceutical assessment.

This randomized, double-blind, controlled, multisite clinical trial was initiated to examine the efficacy of a novel magnetic treatment device as adjunctive therapy for knee pain in patients with RA. Principal outcome measures included patients' reported pain intensity during MagnaBloc™ therapy,[a] as recorded in a pain diary, compared with their initial level of pain. Previous studies have not adequately examined the duration of the effect after application of a magnetic field. Thus, the degree, rapidity of onset, and the duration of relief were also assessed. The study was also aimed at determining whether the level of physical functioning increased in patients who received MagnaBloc therapy as compared with those treated with control devices.

The MagnaBloc is a noninvasive device with no known significant risks. Pilot studies support its efficacy in treating mechanical LBP,[11] as well as pain secondary to RA of the knee.[12] The magnetic field produced by the MagnaBloc reversibly blocks action potential firing by adult dorsal root ganglion cells in monolayer cell culture.[14-16]

METHODS

MagnaBloc Devices

The MagnaBloc is a nonpharmacologic, noninvasive, quadrapolar static magnetic device with 4 permanent center charged, rare earth magnets arrayed with alternating polarity in a hypoallergenic plastic case. It is approximately 3.5cm in diameter, weighs approximately 30g, and generates magnetic fields of about 190mT over each pole. Much larger time-invariant magnetic fields, such as those produced by magnetic resonance imaging (MRI) devices, have not been shown to be harmful to humans or animals.[17-19]

1900 gauss

The magnetic field produced by the square array of the magnets (neodynium-iron boron) penetrates 5cm into cadaveric tissue, as determined with a hand-held gauss meter. The field produced contains regions of steep gradients (0.1–40T/m) in the range found at the aperture of clinically used MRI machines. There is a magnetic flux return ring on the nontreatment side, which maximizes the flux to the treatment site.

Control Devices

The control devices were assembled at the same factory as the MagnaBloc, and were designed to be indistinguishable from the MagnaBloc devices in size, shape, material, and balance. A 0.5-mm steel plate was placed in the plastic MagnaBloc case with 3 aluminum "blanks" and 1 neodynium magnet in place of the quadrapolar MagnaBloc array. A sheet of lead was also enclosed to give the control device a mass identical to that of the MagnaBloc. This configuration results in a unipolar magnetic field against the patient in contrast to the MagnaBloc's quadrapolar alternating array. The field is further dampened by the steel plate, resulting in a maximum field strength at the surface of 72mT and no areas of alternating polarity.

A study with a nonmagnetic placebo, in which the blind could not be maintained, would invalidate the placebo treatment. It was decided that protecting the blind would yield more valid information about the therapeutic potential of the 2 devices. Therefore, a magnetic control device was selected over a nonmagnetic placebo device to ensure the study's blinded nature.

Study Subjects

Volunteers included patients over age 18 years with RA and persistent knee pain despite appropriate use of medications. Subjects had to meet the following criteria: active RA as defined by the American Rheumatism Association's 1987 Revised Criteria for the Classification of Rheumatoid Arthritis[20]; pain related to joint use; functional impairment; clinical evidence of inflammation (heat, swelling, effusion); and no significant change in medical treatment during the study period. Magnetic fields produced by the MagnaBloc can interfere with cardiac pacemakers. Additionally, the device's safety for pregnant women has not been established. Morbid obesity results in technical difficulty encountered both in affixing the devices and in field penetration of the fat layer that surrounds the nerve structure in question. Thus, subjects were excluded if they met any of the following criteria: diagnosis of malignant disease; under 18 years of age; pregnant; severe or unstable neurologic deficit, including demyelinating disease or symptomatic herniated vertebral disk; pacemaker or prosthesis that might be adversely affected by a magnetic field; acute direct trauma by history or on examination; morbid obesity; history of bilateral total knee arthroplasty (resulting in no natural joint for study); history of receiving injections in the affected knee within 6 weeks before the study period; active unresolved litigation; prisoner; or unwilling to abide by the protocol. There is a precedent for including only those patients with a baseline pain score of 40/100mm or greater.[21,22] Patients with a low level of pain at the outset do not experience a significant reduction in their pain intensity. Thus, volunteers were excluded by their pain level as patients with minimal pain, defined as less than 40mm/100mm on a visual analog scale (VAS), do not have pain sufficient to determine whether the treatment is efficacious.

Assessments

Study design followed the American College of Rheumatology's (ACR) recommended core set of disease activity measures for RA clinical trials.[20,23] The following assessments were made: (1) rheumatologist's global assessment of disease activity (R-GADA), (2) Westergren erythrocyte sedimentation rate (ESR) or C-reactive protein, (3) range of motion (ROM) of the knee by goniometry, (4) examination for tenderness, (5) examination for swelling, (6) patients' assessment of physical function, (7) 100mm VAS score for pain, (8) subjects' global assessment of disease activity (S-GADA), (9) the Modified Health Assessment Questionnaire (MHAQ) for difficulty in daily activities,[24,25] and (10) subjects' assessment of treatment outcome. The MHAQ is a standardized set of 8 questions about activities of daily living (ADLs) to which subjects respond that they can accomplish tasks such as buttoning a shirt or turning on a faucet without difficulty (1 point), with some difficulty (2 points), with great difficulty (3 points), or only with help (4 points). Each respondent's points are tabulated and divided by 8, yielding a MHAQ score ranging between 1 and 4.[26]

This study was conducted with the approval of the Vanderbilt University Committee for the Protection of Human Sub-

jects and the Osaka University Medical Center Board of Ethics for Clinical Research.

Statistical Methods

Continuous variables were analyzed by nonparametric methods, using the Wilcoxon signed-rank test (changes in pain intensity of VAS) or the Mann-Whitney *U* test (MHAQ, S-GADA, R-GADA). Chi-square analysis was completed on the dichotomized subjects' assessment of treatment outcome and dichotomized change in pain results.

Procedures

MagnaBloc and control devices were packaged 4 each in identical boxes, which were labeled with consecutive numbers by a research assistant not involved in this study. Assignment of MagnaBloc or control devices to each consecutively numbered box was determined by computerized coin flip. Consecutive patients with RA who met inclusion criteria and who consented to participate were enrolled. A standard examination of the joints, including assessment of tenderness and swelling and measurement of ROM by goniometry, was done by rheumatologists. A global assessment of disease activity (R-GADA) was made by placing a mark on a 100-mm line. The left end of the line indicated no disease while the right end indicated greatest disease severity. Patients reported baseline levels of pain on a pain VAS, and completed the MHAQ, the S-GADA, and subjects' assessment of physical functioning. Westergren ESR and/or C-reactive protein were also assessed.

With the patient seated and the leg flexed 90° at the knee, 4 blinded devices were applied over the suprapatellar and infrapatellar bursae, and over the medial collateral and the lateral collateral ligaments to cover broadly joint swelling and inflamed synovium (fig 1). Devices were affixed to the skin around the joint by double-stick adhesive tape and reinforced with Transpore™ tape[b] over each device. At baseline (before treatment), 1 hour, 1 day, and 1 week after placement of the devices, MHAQ, VAS, and all other baseline questionnaires were repeated. Subjects were instructed to leave the devices taped in place until the 1-week follow-up visit. In addition to the measurements at the 4 time points listed above, each subject was given a 7-page pain diary consisting of 2,100-mm lines per page and instructed to rate the level of pain in the treated joint on awakening and before going to sleep each day. The left end of each line was labeled "no pain," and the right "pain as bad as can be." One week after placement of devices, subjects were reassessed with Westergren ESR and C-reactive protein, MHAQ, VAS, as well as R- and S-GADA; the rheumatologist's examination was repeated in the same manner as at baseline.

At the 1-week follow-up visit, subjects returned the pain diary and blinded devices were removed; examination confirmed that the subjects had left the blinded devices in place. At this time, all subjects were offered true MagnaBloc devices for continued use. The code numbers identifying MagnaBloc and control devices were not broken until all patients completed the study. At study completion, all poles of each device were tested with a hand-held gauss meter; all fields at the device surfaces were within the parameters for MagnaBloc and control devices as detailed in Methods, confirming that there was no deterioration in field strength.

All explanations and instructions given to Japanese patients and physicians were identical to those given to American subjects and physicians. However, informed consent, MHAQ, pain dairies, and rheumatologists' data collection forms were translated into Japanese.

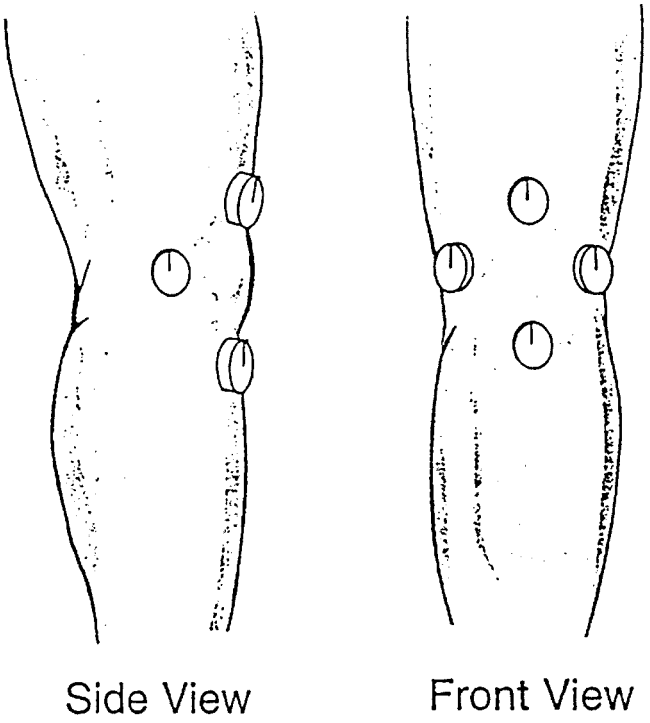


Fig 1. Placement of devices.

RESULTS

Demographics

The trial enrolled a cohort of 64 patients who presented with knee pain to their rheumatologists from October 1998 through May 1999. The 6 centers participating in the study were: the private rheumatology office of Medical Specialists of Nashville; the Arthritis and Joint Replacement Center at Vanderbilt University Medical Center in Nashville, TN; the Osaka University Medical Center Department of Medicine III; and Yukioka Hospital, Toda Clinic, and Hino Hospital in Osaka, Japan.

Of 64 patients with a baseline pain score of 40/100mm or greater, 38 were randomly assigned to the MagnaBloc treatment group, and 26 were randomly assigned to the control group. The 2 cohorts were similar in age, gender, race, duration of disease, level of independent ADLs as assessed by MHAQ, baseline level of pain, and degree of satisfaction with their quality of life (table 1).

Changes in Pain Intensity

Baseline pain levels of 63/100 and 61/100mm were reported by the MagnaBloc and control groups, respectively. At the 1-day follow-up, the MagnaBloc group showed a greater reduction in joint pain than did the control group (31.4% vs 26.5% reduction); this reduction was sustained at the 1-week follow-up (40.4% vs 25.9%). This greater reduction in pain at each time point was corroborated by the diary entries made twice daily, even considering daily pain fluctuations throughout the study (fig 2).

Comparison of each groups' average changes in pain intensity with respect to their baseline level of pain shows a high level of significance ($p < .0001$). However, comparison of the change in pain intensity between the 2 groups shows a statis-

Table 1: Demographics of Randomized Subjects With Baseline Pain 40/100mm

Randomized Group	MagnaBloc (n = 38)	Control (n = 26)
Gender (M/F)	5/33	3/23
Race		
Caucasian	17	6
Japanese	17	19
African American	4	1
Average age (yr)	59.5	61.4
Average duration of RA (yr)	11.8	11.8
Average baseline MHAQ	1.6	1.4
Average baseline pain	63/100mm	61/100mm
Satisfaction with activities		
Very satisfied	3%	4%
Somewhat satisfied	22%	24%
Somewhat dissatisfied	41%	40%
Very dissatisfied	35%	32%

Abbreviations: M, male; F, female.

tically insignificant difference between the effect seen in the MagnaBloc and the control groups ($p < .23$).

Subjects' Global Assessment of Disease Activity

Subjects in the MagnaBloc group reported an average GADA of 63.2/100, 53.0/100, 55.3/100, and 46.7/100mm at baseline, 1 hour, 1 day, and 1 week, respectively. This corresponds to an average decrease in S-GADA of 33% over 1 week. In contrast, the control group reported a significantly smaller decline in self-reported disease severity at these time intervals, from 61.4/100 to 59.3/100 to 59.5/100 to 59.4/100mm, corresponding to a 2% decline over 1 week (fig 3). At 1 week, S-GADA showed significant reduction in the MagnaBloc group compared with the control group ($p < .01$).

Modified Health Assessment Questionnaire

Pretreatment scores on the MHAQ averaged 1.6 and 1.4, respectively, in the MagnaBloc and control groups. After 1 week, MHAQ scores decreased 3% on average in the MagnaBloc group and increased 6% on average in the control group ($p < .15$).

Rheumatologist's Global Assessment of Disease Activity

The R-GADA revealed greater disease severity in the MagnaBloc group at the outset, averaging 49.0/100 versus 43.0/100mm in the control group. There was an average reduction of 16.7mm in the MagnaBloc group and 7.5mm in the control group, yielding a less severe disease severity in the MagnaBloc group after 1 week. These changes reflect a R-GADA decline of 14% in the MagnaBloc group and 7% in the control group. This difference between the groups showed a trend, but remained statistically insignificant ($p < .18$).

Serum Analysis for Acute Phase Reactants

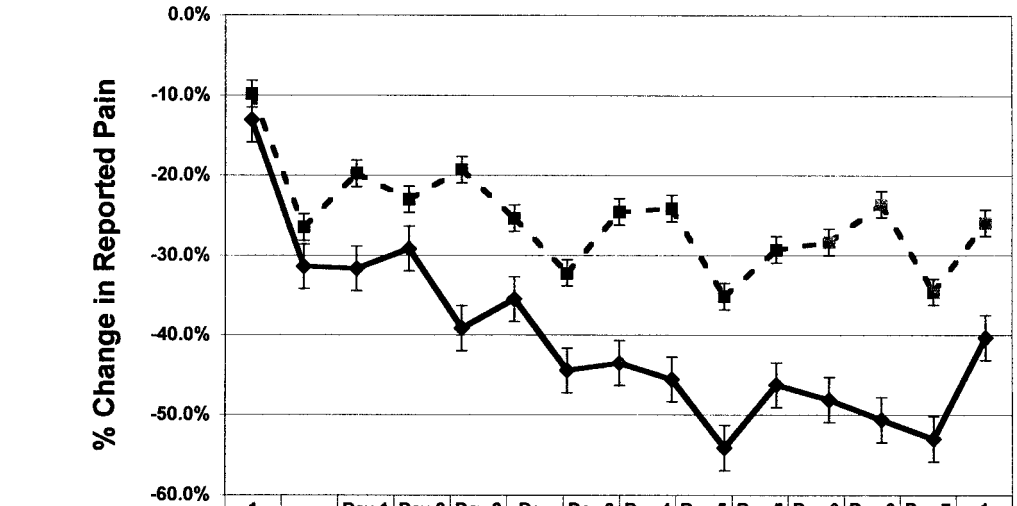
In the MagnaBloc group, average ESR results rose from 43.8 pretreatment to 45.5 at 1 week, and average C-reactive protein levels rose from 4.25 to 4.35. In the control group, the ESR results were 41.9 before treatment and 39.3 at 1-week follow-up, and average C-reactive protein levels were 2.6 at both measurements. Thus, on average, there was not a significant change in acute phase-reactant levels.

Rheumatologist Joint Examination

On average, there were no significant differences in point tenderness, swelling about the joint, or ROM of the joint (average change, 113°–115° in MagnaBloc group; 123°–122° in control group by goniometry).

Subjects' Assessment of Treatment Outcome

After 1 hour, 1 day, and 1 week of treatment with the blinded devices, subjects completed a questionnaire comparing pain levels before and after treatment. At 1 hour, 39% of both groups reported feeling better or much better, while 58% of the MagnaBloc group and 62% of the control group reported feeling the same. After 1 day, 47% of the MagnaBloc group and 35% of the control group reported feeling better or much better while 40% and 60%, respectively, reported feeling the same. This trend continued at 1 week, with 68% of the MagnaBloc group and 27% of the control group reporting feeling



	1 Hour	1 Day	Day 1 PM	Day 2 AM	Day 2 PM	Day 3AM	Day 3 PM	Day 4 PM	Day 5 AM	Day 5 PM	Day 6 AM	Day 6 PM	Day 7 AM	1 Week
MagnaBloc	-13.1	-31.4	-31.7	-29.2	-39.2	-35.5	-44.5	-45.6	-54.1	-46.3	-48.1	-50.6	-53.0	-40.4
Magnetic Placebo	-9.8%	-26.5	-19.8	-23.0	-19.3	-25.4	-32.2	-24.1	-35.2	-29.3	-28.4	-23.6	-34.6	-25.9

Fig 2. Average percentage change in pain. NOTE. $p < .0001$ at 1 week for each group compared with baseline. $p = .23$ comparing the difference between groups at 1 week. Error bars indicate the standard error at each time point.

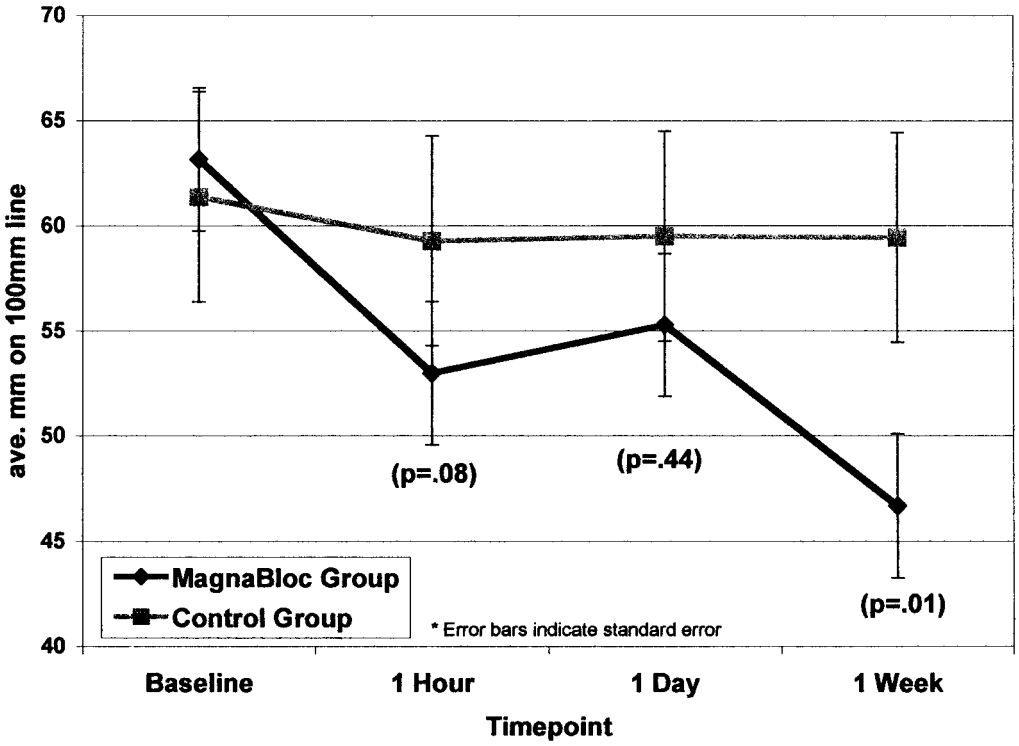


Fig 3. Subjects' global assessment of disease activity.

better or much better. At the study's conclusion, 29% of the MagnaBloc group and 65% of the control group reported feeling the same as before treatment (fig 4). The difference in reported improvement in the MagnaBloc group at 1 week was statistically significant ($\chi^2 = 10.64$, $p = .001$).

The field strengths of all poles of each blinded device were tested after the study was concluded, confirming that all MagnaBloc and control devices had a field strength within parameters and was uniform between devices. Thus, all patients in the study received a standardized treatment.

DISCUSSION

RA is a chronic, progressive inflammatory disease of idiopathic origin. The ACR has established criteria for evaluation of RA patients in clinical trials.[23] We used several assessments in this study, the outcome of which shows that some criteria

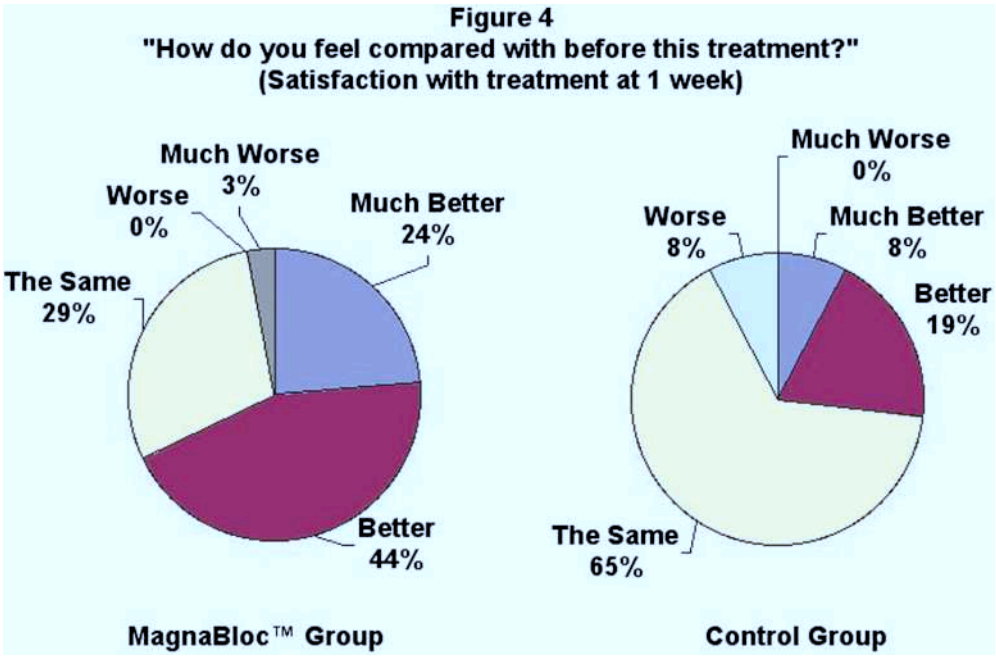


Fig 4. Subjects' assessment of treatment outcome at 1 week.

Table 2: Tabular Summary of Results and Statistical Significance Values

	MagnaBloc ($n = 38$)	Control Device ($n = 26$)	p (baseline vs 1wk)
	Pain Reduction in mm (mean ± SD) (fig 2)		
Baseline	63.0 ± 14.5	61.0 ± 15.6	
Pain reduction at 1hr	−10.9 ± 27.2	−5.9 ± 18.6	
Pain reduction at 1d	−17.8 ± 24.1	−22.9 ± 28.2	
Pain reduction at 1wk	−24.5 ± 25.5	−16.3 ± 21.4	<.0001 for each <.23 b/w groups
	Dichotomized Pain Reduction at 1wk (% of subjects)		
Pain improved	$n = 18$ (47%)	$n = 8$ (31%)	
Pain not improved	$n = 20$ (53%)	$n = 18$ (69%)	
	χ^2 (1df) = 1.76, $p < .18$		
	R-GADA and S-GADA (fig 3)		
R-GADA change	−16.7mm (−14%)	−7.5mm (−7%)	<.18
S-GADA change	−19.9mm (−33%)	−4.2mm (−2%)	<.01
	Subjects Assessment of Treatment Outcome at 1wk (fig 4)		
Better/much better	26 (68%)	7 (27%)	
No change	11 (29%)	17 (65%)	
	$\chi^2 = 10.64$, $p < .001$		
	MHAQ Change		
MHAQ	−3%	+6%	<.15

may be more sensitive than others for assessing knee pain in RA. For example, S-GADA and subjects' assessment of treatment outcome with respect to physical functioning showed significant improvement at 1 week in the MagnaBloc group in comparison with the control group. The reductions in S-GADA and R-GADA were of similar raw magnitude, but of differing proportion (table 2), reflecting differing perceptions among subjects and rheumatologists. It is not surprising that it was the S-GADA that demonstrated a statistically significant difference, because this index is most responsive to change in large placebo-controlled trials of disease-modifying antirheumatic drugs, with a relative efficiency compared with tender joint count of 1.88.[27]

Another important index is the patient's perceived improvement. In this trial, a significantly greater percentage of patients in the MagnaBloc treatment group reported improvement. In office practice, among the most trusted measures guiding titration of drug dosages is the patient's perception of treatment outcome. This study was designed to incorporate this dimension, in addition to the ACR suggested instruments. This demonstrated a highly significant treatment outcome, showing it to be possibly more sensitive to changes than the R-GADA. The importance of the patients' assessments of their functioning should be considered along with the ACR's core disease activity measures for RA clinical trials, considering the difficulties in measuring outcomes in this idiopathic disease known for its fluctuating course.

In analyzing the pain data (fig 2), there is a visible difference in the trends for MagnaBloc and control device groups by a factor of approximately 1.5. However, because of wide variance in pain level responses in the control group, a trend analysis did not show a significant difference despite the visible difference in the averages. It is also notable that pain at the 1-week follow-up was consistently rated higher than before coming to the clinic on day 7. This increase in pain level may be related to the effort required of RA patients to combine walking with taking taxis, buses, and trains in going to the clinic. Our subjects had different access to transportation and traveled as little as 10 minutes and as long as 2 hours to reach the clinic.

As seen in this trial, the ACR's criteria for evaluation in RA clinical trials may not be appropriate for assessment of localized treatment of a knee. For example, the MHAQ, with only 1 of the 8 questions related to knee function, did not show significance. However, patients responded in a follow-up questionnaire 3 months later that they could come to clinic more easily, were more functional in walking, and felt greater ease in ambulation; with use of the MagnaBloc, their life was less limited by the knee pain. This was true for patients using the MagnaBloc, whether or not they were in the original treatment group. Thus, future studies, expanded beyond 1 week may give a better sense of the MagnaBloc's therapeutic potential.

In this trial, significant improvements in VAS and R-GADA were also shown by comparing baseline and 1 week assessments in each group. However, only a trend suggesting a relationship was shown when treatment groups were compared. The VAS may not be a sensitive enough instrument, due to variability in assessment, inadequate size, and/or differing size of the treatment and control groups, and the general insensitivity of the VAS.[28,29] It may be even less sensitive to reductions in pain intensity than to unchanged or increased pain, especially if pain is not completely relieved.[21] It is possible that a larger number of subjects in each group would have overcome such insensitivity of the VAS. Additionally, with small numbers, each subject has a disproportionate effect on the overall outcome. In future studies, a well-informed power analysis should be performed to assess more accurately an appropriate sample size, considering the insensitivity of the VAS. It is also possible that a multicomponent assessment of pain, such as the Western Ontario and McMaster Universities Osteoarthritis Index,[30] would allow corroboration among various pain indices, so that the pain assessment would not depend so heavily on 1 index. Another option would be to use algometry to assess subjects' levels of pain to supplement the VAS.

A major challenge inherent in studying therapeutic effects of magnets is the selection of an appropriate placebo for compar-

ison. In this trial, there was a significant reduction in self-reported pain in both treatment groups. However, there was not a statistically significant difference in reduction of pain with the MagnaBloc compared with the magnetic control device. One reason may be the use of a magnetic control, rather than a nonmagnetic placebo device. Without a comparison with a device devoid of a magnetic field, it is unclear whether even a weak magnetic field may have had a therapeutic effect. In a study of the placebo response, Long et al[31] showed that 14% of patients exposed to sham magnet therapy demonstrated a 50% or greater reduction in pain. In our study, if dichotomized by criteria used by Long, respondents being defined at 50% reduction in pain or greater, 54.8% of the MagnaBloc group and 32% of the control group responded to treatment. Thus, our control group did not correlate with the placebo response shown by Long, and therefore most likely cannot be considered a placebo group. In this study, we did not select a true placebo, but rather a control device that has not been validated as a placebo. In future studies, we hope to employ a more definitive placebo device. Because this study compared 2 devices with magnetic field gradients, it was really a dose-comparative study.

It is possible that the characteristics of the MagnaBloc may not have been ideally suited to the treatment of RA because the pain generators were not identified and it is not known if the MagnaBloc is strong enough to reach those sites. It is possible that a stronger field with deeper tissue penetration may have had more of an effect. In addition to the unknowns inherent in a study of a poorly understood disease, the constitution of the treatment groups was mixed and the ratio of Japanese to American subjects differed. We could not control for the theoretical varying cultural differences in interpretation of pain, but there was no significant difference between Japanese and non-Japanese responses. Furthermore, contralateral knee tenderness, inflammation, and ROM were assessed by the rheumatologist at each time point. However, subjects were not questioned about pain in the contralateral knee. Thus, it is not known whether subjects adequately differentiated between pain in the treated and nontreated knees.

Research by our group established a basis for the clinically observed reduction in pain. Exposure to the fields causes reversible blockade of action potential firing and reduction of responses to the pain-producing substance capsaicin in cultured adult dorsal root ganglion.[14-16] The array of 4 permanent magnets of alternating polarity in each MagnaBloc device produce magnetic fields with regions of steep gradients that, in cell culture, block firing of sodium-dependent action potentials of sensory neurons.[14-16] Additionally, a spatially homogenous static magnetic field has been shown to reversibly reduce calcium current in the pituitary-derived lactosomatotrophic (GH3) cell line.[32] The molecular mechanism of these effects has not been fully established, but may involve conformational changes in the ion channels and/or neuronal membrane. Considering the time required for the effect on action potentials, multiple mechanisms must be acting simultaneously, possibly including indirect effects, such as reduction in activity of channel phosphorylating enzymes.

CONCLUSION

The results of this randomized, double-blind, controlled, multicenter clinical trial indicate a probable superiority of the magnetic field generated by the MagnaBloc over that produced by a control magnetic device. In this trial, the MagnaBloc was compared with a device that had greatly differing field geometry and maximal field strength. When normalized and analyzed by nonparametric statistical tests, both devices were significantly effective in reducing pain and in improving patients' overall disease severity; there was not, however, a statistically significant difference between the 2 groups for percentage of pain reduction. There was a statistically significant difference between groups for S-GADA and subject functional assessment of treatment outcome.

In addition to the clinical outcomes measured, this study was useful in elucidating better methods for conducting clinical trials with magnetic devices. Certain instruments used did not give an adequate picture of what we were treating. Specifically, the R-GADA and MHAQ are not validated for studying localized knee pain. The trends that we found justify further study. As we refine the instruments used, we will be better able to assess the true effects of treatment.

Last, the rationale for use of a magnetic control device was to maintain the blind, which we did successfully. However, possibly because of our selection of a magnetic control, both devices were significantly efficacious in reducing pain from baseline of the respective treatment groups. Further studies, employing a validated placebo device, a larger sample size, and more appropriate instruments to assess localized pain and function are warranted.

References

1. Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray WA. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. Ann Intern Med 1991;114:257-63.
2. Gurwitz JH, Avorn J, Ross-Degnan D, Lipsitz LA. Nonsteroidal anti-inflammatory drug-associated azotemia in the very old. JAMA 1990;264:471-5.
3. Macklis RM. Magnetic healing, quackery, and the debate about the health effects of electromagnetic fields. Ann Intern Med 1993;118:376-83.
4. Trock DH, Bollet AJ, Dyer RH, 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.
5. Colbert AP, Markov MS, Banerji M, Pilla AA. Magnetic mattress pad use in patients with fibromyalgia: a randomized double-blind pilot study. In: Potential Therapeutic Applications of Magnetic Fields, International Symposium of the Bioelectromagnetics Society; 1999 Nov 15-16; Nashville, TN.
6. Washnis GJ. Discovery of magnetic health: a health care alternative. Wheaton (MD): Health Research Publishers; 1998.
7. Borsa PA, Liggett CL. Flexible magnets are not effective in decreasing pain perception and recovery time after muscle microinjury. J Athl Train 1998;33:150-5.
8. Collacott EA, Zimmerman JT, White DW, Rindone JP. Bipolar permanent magnets for the treatment of chronic low back pain. JAMA 2000;238:1322-5.
9. Vallbona C, Hazlewood CF, Jurida G. Response of pain to static magnetic fields in postpolio patients: a double-blind pilot study. Arch Phys Med Rehabil 1997;78:1200-3.
10. Weintraub MI. Magnetic biostimulation in painful diabetic peripheral neuropathy: a novel intervention—a randomized, double-placebo crossover study. Am J Pain Manage 1999;9(1):8-17.
11. Holcomb RR, Parker RA, Harrison MS. Biomagnetics in the treatment of human pain—past, present, future. Environ Med 1991;8:24-30.
12. Segal N, Huston J, Fuchs H, Holcomb R, McLean M. Efficacy of a static magnetic device against knee pain associated with inflammatory arthritis. J Clin Rheumatol 1999;5:302-4.
13. Weinberger A, Nyska A, Giler S. Treatment of experimental inflammatory synovitis with continuous magnetic field. Isr J Med Sci 1996;32:1197-201.
14. McLean MJ, Holcomb RR, Wamil AW, Pickett JD. Effects of steady magnetic fields on action potentials of sensory neurons in vitro. Environ Med 1991;8:36-44.
15. McLean MJ, Holcomb RR, Wamil AW, Pickett JD, Cavopol AV. Blockade of sensory neuron action potentials by a static magnetic field in the 10 mT range. Bioelectromagnetics 1995;16:20-32.

16. Cavopol AV, Wamil AW, Holcomb RR, McLean MJ. Measurement and analysis of static magnetic fields the block action potentials in cultured neurons. Bioelectromagnetics 1995;16:197-206.
17. Edelman RR, Warach S. Magnetic resonance imaging (1). N Engl J Med 1993;328:708-16.
18. Villa M, Mustarelli P, Caprotti M. Biological effects of magnetic fields. Life Sci 1991;49:85-92.
19. Repacholi MH, Greenebaum B. Interaction of static and extremely low frequency electric and magnetic fields with living systems: health effects and research needs. Bioelectromagnetics 1999;20: 133-60.
20. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
21. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA 1998;280:1831-6.
22. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA 1998;280:1837-42.
23. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. Arthritis Rheum 1993;36:729-40.
24. Pincus T, Summey JA, Soraci SA, Wallston KA, Hummon HP. Assessment of patient satisfaction in activities of daily living using a modified Stanford health assessment questionnaire. Arthritis Rheum 1983;26:1346-53.
25. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.
26. Buchbinder R, Bombardier C, Yeung M, Tugwell P. Which outcome measures should be used in rheumatoid arthritis clinical trials? clinical and quality of life measures responsiveness to treatment in a randomized controlled trial. Arthritis Rheum 1995; 38:1568-80.
27. Tugwell P, Wells G, Strand V, Maetzel A, Bombardier C, Crawford B, et al. Clinical improvement as reflected in measures of function and health-related quality of life following treatment with leflunomide compared with methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 2000;43:506-14.
28. Chapman CR, Casey KL, Dubner R, Foley KM, Gracely RH, Reading AE. Pain measurement: an overview. Pain 1985;22:1-31.
29. Carlsson AM. Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analog scale. Pain 1983;16: 87-101.
30. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833-40.
31. Long DM, Uematsu S, Kouba RB. Placebo responses to medical device therapy for pain. Stereotact Funct Neurosurg 1989;53: 149-56.
32. Rosen AD. Inhibition of calcium channel activation in GH3 cells by static magnetic fields. Biochem Biophys Acta 1996;1282: 149-55.

Suppliers

a. MagnaBloc, 1500 21st Ave S, Ste 1516, Nashville, TN 37212.
b. 3M, 3M Center, St Paul, MN 35144-1000.