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A 3-month, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of a highly optimized, capacitively coupled, pulsed electrical stimulator in patients with osteoarthritis of the knee[1]

D. Garland M.D., Director†, P. Holt M.D., Assistant Professor of Medicine‡,
J. Timothy Harrington M.D., Associate Professor of Medicine§*[a],
J. Caldwell M.D., Medical Affairs‖, T. Zizic M.D., Associate Professor of Medicine‡[a] and
J. Cholewczynski B.S., Independent Clinical Statistician
† *Division of Neurotrauma, Rancho Los Amigos Medical Center, USA*
‡ *Johns Hopkins School of Medicine, Baltimore, MD, USA*
§ *University of Wisconsin School of Medicine and Public Health, Madison, WI, USA*
‖ *BioniCare Medical Technologies, Inc., USA*

Summary

Objective: To investigate the efficacy and safety of a capacitively coupled, pulsed electrical stimulation device in treating knee osteoarthritis (OA).

Design: Fifty-eight outpatients with moderate to severe OA of the knee entered a 3-month, double-blind, placebo-controlled trial, using either an active or placebo device at home for 6 to 14 h/day. Outcome measures included a patient global evaluation, a patient report of knee pain severity, and the Western Ontario and McMaster Universities (WOMAC) questionnaire.

Results: Active treatment provided superior outcomes between baseline and 3-month follow-up measurements: 50.6% greater improvement than placebo in patient global ($P = 0.03$), 31.2% in patient pain ($P = 0.04$), 25.1% in WOMAC stiffness ($P = 0.03$), 29.5% in WOMAC function ($P = 0.01$), 19.9% in WOMAC pain ($P = 0.11$), and 27% in total WOMAC ($P = 0.01$). The percent of patients who improved by more than 50% was 38.5 active vs 5.3 placebo in patient global ($P = 0.01$), 43.6 vs 15.8 in patient pain ($P = 0.04$), 38.5 vs 10.5 in WOMAC pain ($P = 0.03$), 28.2 vs 5.3 in WOMAC stiffness ($P = 0.08$), 23.1 vs 5.3 in WOMAC function ($P = 0.14$), and 23.1 vs 5.3 in total WOMAC ($P = 0.14$). Twenty-one percent of placebo and 18% of actively treated patients developed a transient rash at the electrode sites. No other adverse device effects were reported.

Conclusion: A highly optimized, capacitively coupled, pulsed electrical stimulus device significantly improved symptoms and function in knee OA without causing any serious side effects.

Key words: Knee osteoarthritis, Pulsed electrical stimulation treatment.

Introduction

Osteoarthritis (OA) of the knee is a degenerative disorder, usually progressive, that results from excessive catabolism and inadequate production of cartilage matrix[1–4]. The consequences of this condition are degeneration in underlying bone, inflammatory responses in the adjacent synovium, and deterioration of other soft tissue structures within the joint. No therapies exist currently that can reverse this process. Nonoperative treatment of knee OA has changed very slightly over the past 40 years. Nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics relieve pain and help knee OA patients function better, but many patients fail or do not tolerate these medications. Hyaluronans work in patients with milder OA of the knee[5]. The role of neutraceuticals such as glucosamine and chondroitin sulfate remains controversial. An National Institutes of Health (NIH)-sponsored trial of glucosamine and/or chondroitin sulfate in knee OA patients failed to show a therapeutic effect of these agents[6]. The withdrawal of Cox II specific NSAIDs rofecoxib and valdecoxib from the market has diminished the number of available nonsurgical therapeutic options. New therapies are needed.

Pulsed electrical stimulation (PES) provides such a new therapy for knee OA, and possibly for other joint diseases as well. An initial, 1-month (78 patients) randomized, double-blind, placebo-controlled trial showed that a prototype device for delivering an optimized PES signal to the knee tissues improved symptomatic knee OA patients' pain and symptoms, physician global evaluation and patient assessment of knee function[7]. The same device enabled 62% of

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[a]Drs Harrington and Zizic are employees of BioniCare Medical Technologies, Inc.
*Address correspondence and reprint requests to: J. T. Harrington, M.D., Rheumatology, Department of Medicine, School of Medicine and Public Health, One South Park Street, Madison, WI 53715, USA. Tel: 1-608-287-2800; Fax: 1-608-287-2316; E-mail: tim.harrington@uwmf.wisc.edu
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103 patients with severe knee OA who had been advised to have total knee arthroplasty (TKA) to defer this surgery for 4 or more years, in contrast to 7% of a comparator group[8,9]. An Food and Drug Administration (FDA) cleared, commercially available version of this device (BioniCare Medical Technologies, Inc., Model BIO-1000™) has provided similar relief of symptoms and improved patient and physician global evaluations in 75% of an additional 288 patients monitored in a phase IV study[10].

The specific characteristics of this optimized PES signal were derived from more than 20 years of research that has explored homeostatic electrical signaling in articular cartilage, the loss of signaling in OA, and the regenerative effect of exogenous PES in animal models of cartilage injury[11–22]. Its precise modes of action in human knee OA have yet to be determined, but *in vitro* signaling of articular cartilage explants has shown increased messenger RNA transcription of genes that promote synthesis of chondrocyte Type II collagen and aggrecan, and suppression of matrix metalloproteinases and interleukin-1[21,22]. This PES is analogous to bone stimulator therapy for fracture nonunion[23], and is not related to the mechanism of action or clinical effects of transcutaneous electrical nerve stimulation devices (TENS)[24].

The present 3-month double-blind controlled study was designed to confirm and extend the previous observations of clinical effectiveness of the BIO-1000™ device in patients with knee OA.

Materials and methods

STUDY POPULATION

Patients with moderate to severe knee OA were offered study participation during regular office visits in two orthopedic surgery and one rheumatology practices beginning in December 2004 and ending in July 2005. No advertising was done. Moderate to severe disease was defined as persistence of pain on NSAID and/or analgesic therapy and the presence of Kellgren–Lawrence Grade 3 or 4 changes on standing, weight bearing, semiflexed X-ray views of the knees[25,26]. Patients with knee instability and/or valgus or varus deformities of $>20^{\circ}$ were excluded.

A total of 103 patients signed informed consent forms. Three patients withdrew prior to randomization due to unwillingness to keep the appointments (one patient) or to use the device as prescribed (two patients). Patients entered at each site were separately randomized as described below under Design and Randomization. All 42 subjects entered by one orthopedic practice were subsequently omitted because many were provided other, often undocumented, new treatments during the study in violation of the protocol. The 58 patients from the two remaining practices are included in the analysis.

Other inclusion criteria included age 18 years or greater, the intellectual ability to understand and sign an informed consent and complete the study questionnaire, and willingness to maintain stable doses of analgesics and NSAIDs for 1 month prior to study entry and during the 3-month double-blind period. Other exclusion criteria were pregnancy, breastfeeding, intention to become pregnant, infectious arthritis, cardiac pacemakers or other implantable electronic devices, a diagnosis of gout, recurrent inflammatory episodes of pseudogout, malignancy (other than basal cell carcinoma) in the prior 3 years, inflammatory arthritis such as rheumatoid arthritis, psoriatic arthritis, Reiter's syndrome, hemochromatosis, inflammatory bowel disease, ankylosing spondylitis, other collagen vascular disease, Paget's disease adjacent to the treated knee, significant instability of the treated knee as determined by the investigator, a history of drug or alcohol abuse within the past 2 years, morbid obesity (defined as a body mass index (BMI) greater than 45), involvement in litigation or Workers' Compensation, intra-articular injection of the target joint within the past month, previous arthroplasty of the treated knee, and arthroscopy in the treated knee within the past 6 months.

DESIGN

This was a 12-week, 2:1 active to placebo, randomized, double-blind trial. The 2:1 ratio was chosen to encourage patient compliance. After signing the informed consent, patients completed two sets of questionnaires, underwent a physical examination, and received education as to device use at two separate baseline visits 1 week apart. Standing, weight bearing, semiflexed X-rays of the knees were also obtained[25]. Stable NSAID and/or analgesic use was maintained 1 month prior to and throughout the study rather than being withdrawn to produce a disease flare.

Subjects' adherence to treatments, including the study device and baseline NSAID and/or analgesic use, was monitored by weekly phone calls from a contract research organization and during 3 monthly follow-up visits with the investigator, at which time examination and questionnaires were also repeated. Hours of use were monitored by a timer within the device, and were recorded during both phone calls and visits. NSAID and analgesic use and device voltage settings were further confirmed by daily diaries.

DEVICE USED

The PES study device consisted of a knee garment with flexible, embedded electrodes and a small battery-operated generator that produced a 100-Hz, negative pulsed signal (Fig. 1). It weighs 8 ounces. Patients were asked to wear the device for 6 h or more each day, usually at night. They first applied a conducting gel to each electrode, then positioned the garment with the negative electrode on the skin over the patella and the positive return electrode over the anterior distal thigh. They then turned on the device, increased the signal amplitude to between 0 and 12 V by rotating a dial until a tingling sensation was felt over the knee or thigh, and then reducing the amplitude until this sensation disappeared. Thus active treatment remained imperceptible and indistinguishable from placebo. The placebo devices shut off after the amplitude was reduced, and further adjustments required all devices to be restarted. All active and placebo devices contain a timer that records the cumulative hours when the device is in use. This PES device is manufactured and sold by BioniCare Medical Technologies, Inc., Sparks, Maryland.

OUTCOME MEASURES

Primary outcome measures were (1) the percent change from baseline on a 0–100 visual analog scale (VAS) measuring patient global evaluation of arthritis symptoms in the treated knee (Question: Considering all the ways your arthritis condition affects you, how are you doing today?), (2) the percent change from baseline on a 0–100 VAS measuring pain and other symptoms in the treated knee (Question: Considering your pain and symptoms in your study joint how are you doing today?), and (3) percent changes

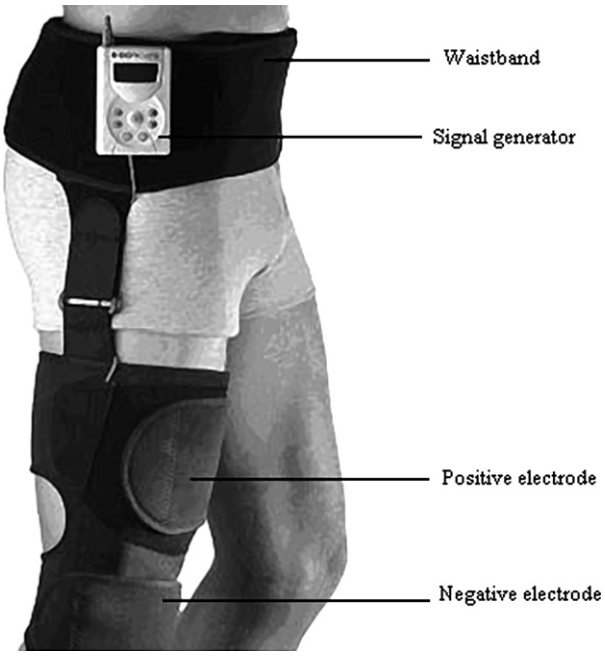

Fig. 1. The PES study device consisted of an optional waistband, a small battery-operated signal generator that produced a 100-Hz, negative pulsed signal, and a knee garment with flexible, embedded electrodes.

from baseline on the Western Ontario and McMaster Universities (WOMAC) pain (0–500), stiffness (0–200), and function (0–850) subscales as measured on 100 mm VASs. Secondary outcomes were the percent of patients that experienced 50% improvement in the patient global evaluation, pain and symptoms in the treated knee, and in the three WOMAC outcome scale measures. The occurrence of rashes and other adverse device effects was solicited and recorded at each visit.

STATISTICAL METHODS

Randomization

Each placebo and active device was assigned a unique number. Each study site was provided both types of devices in a ratio of two active to one placebo. A master random number chart was generated and maintained by an independent observer who had no interaction with the sponsors, primary investigators or patients. As patients signed informed consents they were assigned a device number serially. The number coincided with active or placebo units according to the dictates of the random number table. The clinical investigators had no influence on the assignment of any specific patient to an active or placebo device. The blind has never been revealed to any of the authors except the statistician.

Baseline characteristics

Baseline values were analyzed by comparing means for each treatment group for continuous variables such as age, VAS or WOMAC outcome scale measurements, or comparing patient counts for each treatment group for discrete variables such as gender. Outcome measures for the two baseline visits were averaged to provide each subject's baseline values. Statistical methods used in analysis were the *t* test for continuous variables or the Fisher's exact test for discrete variables.

Outcome measures

Percent changes from baseline to the final visit on the VAS and WOMAC scale were calculated as follows:

$$\frac{(\text{Baseline average} - \text{month three score}) \times 100}{\text{Baseline average}}$$

Fisher's exact test was used to compare gender, percent of patients using assistive devices, need for TKA and $\geq$50% responses in efficacy outcomes at the final visit between active- and placebo-treated patients. Student's *t* test was used to compare percent changes in outcome measures between the baseline and final visits. Student's *t* test was also used to compare differences between treatments for age, BMIs and years diagnosed.

Distribution of Kellgren–Lawrence scores between groups was compared using the χ^2 test. SAS software, version 9 was used to perform the statistical analysis.

Missing values

Two patients, one placebo and one active device treated, discontinued study participation before the second month follow-up visit. In both cases the missing outcomes at 3 months were imputed by last observation carried forward (LOCF).

Data analysis

A contract research organization monitored the study, and an independent statistician examined and statistically evaluated the data results. The investigators did not see the original data sets.

INSTITUTIONAL REVIEW BOARD APPROVAL

The Independent Investigational Review Board approved the study.

EXPLORATORY ANALYSES REQUESTED DURING REVIEW

Total WOMAC scores were not a defined outcome in the protocol, but are shown in Tables II(a)–(d). The number of patients in the active and placebo groups showing 50% improvement in one to six of the primary measures and total WOMAC were also tabulated.

Results

PATIENT POPULATION BASELINE CHARACTERISTICS

Fifty-eight subjects were randomized to therapy. Tables I(a) and (b) show their baseline demographics, use of medicines and assistive devices, whether treating physicians considered them to be a candidate for TKA, and their baseline disease severity measures. Subjects in each treatment group were equivalent as to age, sex, BMI, baseline antiarthritic medical therapy and Kellgren–Lawrence X-ray score. Those in the active group showed more severe patient global evaluation scores ($P = 0.04$), but otherwise disease severity was comparable. No explanation for this disparity other than chance is apparent. The patients from rheumatology and orthopedic practices were similar in both

Table I(a)
Baseline characteristics by treatment group. No statistically significant differences were present between active- and placebo-treated patients

Characteristic	Active ($N=39$)	Placebo ($N=19$)	Total ($N=58$)
Gender			
Male, no. (%)	12 (30.8)	8 (42.1)	20 (34.5)
Female, no. (%)	27 (69.2)	11 (57.9)	38 (65.5)
Age, years (standard deviation)	64.3 (10.2)	69.9 (11.4)	66.1 (10.9)
Medication requirements			
Analgesics alone (%)	28.2	26.3	
NSAIDs alone (%)	59.0	47.4	
Analgesics + NSAIDs (%)	12.8	26.3	
Years diagnosed, mean (range)	9.0 (0.8–44.0)	7.2 (0.2–20.0)	8.4 (0.2–44)
BMI, mean (range)	31.3 (20–43)	30.2 (22–41)	31.2 (20–44)
Use of assistive devices, no. (%)	5 (12.8)	4 (21.1)	9 (15.5)
Total knee surgery candidates	28 (71.8)	13 (68.4)	41 (70.1)

baseline outcome measures and Kellgren–Lawrence X-ray grades.

OUTCOME MEASURES

Table II(a) shows the differences between the active and placebo groups' percent changes from baseline to the 3-month visit for each primary outcome measure, and for total WOMAC scores as well. Analyses of differences between treatment groups were statistically significant for five of these six outcome measures: patient global, patient pain, WOMAC stiffness, WOMAC function, and total WOMAC. Only the WOMAC composite pain scale difference was not significant. The study data are also presented in Tables II(b)–(d) as raw scores (mm), differences from baseline (mm), and percent changes from baseline, all expressed as the mean ± standard deviation.

Figure 2 shows the percent of patients in each treatment group who experienced 50% or greater improvement in each primary outcome measure. Three of five primary outcome measures showed a significant difference between active and placebo groups, and a small percent of placebo patients showed a 50% change in each measure. The exceptions were WOMAC stiffness ($P=0.08$) and function ($P=0.14$). The total WOMAC was at least 50% improved in 23.1% of active and 5.3% of placebo patients, but did not reach significance ($P=0.14$). Twenty-one of 39 actively treated patients improved by 50% in at least one outcome measure vs five of 19 placebo patients. Ten active and no placebo patients improved 50% in four to six measures. The 18 active patients who had no 50% responses did not differ in their hours of treatment from those who did. Valid statistical testing of these trends was not possible.

Table III shows that hours of use were similar in the two treatment groups. The placebo patients used the device for a mean of 656 ± 193 h (range 310–1052), and the active patients for 692 ± 187 h (range 0–1019) ($P=0.52$). The hours of use for each group were normally distributed, and the Shapiro–Wilk W statistic was >0.90. About 60% of each group achieved an average use of 6 h or more per day.

The voltage amplitude that patients dialed into their devices could range from 0 to 12 V. Actual mean amplitudes were 4.7 ± 1.1 V for the placebo-treated group and 4.1 ± 0.98 V for the active group ($P=0.03$). The amplitudes were normally distributed. This small 0.6 V difference is electronically meaningless and could not influence the outcome differences between the two groups. The slightly higher signal amplitudes delivered to the placebo patients were delivered for less than 5 min after the device setup each day.

ADVERSE DEVICE EFFECTS

A skin rash developed at the site of electrode placement in 21.1% of placebo and 17.9% of active patients ($P>0.05$). These were usually transient and required only local topical therapy, stopping device use for a few days, and/or a change in the conducting gel. Previous studies and post marketing clinical observations indicate that most rashes are due to the conducting gel. No systemic

Table I(b)
Comparison of baseline disease severity characteristics between active- and placebo-treated patients. Patient global evaluation was worse at baseline for the participants in the active group ($P=0.04$). No other statistically significant differences between groups were present

	Active	Placebo
Outcome measures*		
Patient global	51.3	41.4
Patient pain	50.9	48.1
WOMAC pain	50.6	44.9
WOMAC stiffness	58.4	53.4
WOMAC function	51.9	44.9
Kellgren–Lawrence X-ray grade, no. of points		
1	0	0
2	0	0
3	20	10
4	19	9

*See Table II(b) for baseline means ± standard deviations.

Table II(a)
Percent change from baseline in efficacy outcome parameters. Percent differences represent differences between active and placebo groups, with all differences favoring active over placebo

Outcome	Difference	P value
Patient global	50.56	0.031
Patient pain	31.20	0.038
WOMAC pain	19.85	0.110
WOMAC stiffness	25.06	0.030
WOMAC function	29.46	0.013
Total WOMAC	26.64	0.014

Table II(b)
Raw mean scores (mm) for active and placebo device groups

	Active ($N=39$)				Placebo ($N=19$)			
	Baseline		3 months		Baseline		3 months	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Patient global	51.3	17.38	38.3	25.81	41.4	16.12	45.1	21.41
Patient pain	50.9	17.99	36.2	26.05	48.1	16.76	45.7	21.76
WOMAC pain	50.6	14.20	37.4	23.60	44.9	12.47	41.8	16.59
WOMAC stiffness	58.4	20.07	43.1	28.59	53.4	16.13	50.1	18.09
WOMAC function	51.9	15.98	39.9	24.59	44.9	14.87	46.6	18.31
Total WOMAC	52.2	14.90	39.6	24.25	45.6	13.32	45.9	16.81

reactions occurred, and no unanticipated adverse device effects were reported.

Discussion

Active PES treatment of these patients with moderate to severe knee OA provided significant and clinically meaningful improvement relative to placebo in four of five primary outcome measures, including the patient global, pain and symptoms, and the WOMAC stiffness and function subscales [Table II(a)]. The total WOMAC score, added to the results at the request of reviewers, was also improved, as would be expected. Only the results of the WOMAC five question pain subscale failed to reach significance ($P=0.11$); however, when 50% or more improvements were compared, active treatment was superior for the WOMAC pain as well, as shown in Fig. 2 ($P=0.03$). No systemic adverse device events appeared in this study. The results of the WOMAC function subscale were also discordant for significant effect between the primary measure ($P=0.013$) and the number of 50% improvers ($P=0.14$), but the latter also favored active over placebo treatment. The inclusion of total WOMAC scores does not alter the significance of results, but does offer a composite of the individual outcomes measures.

Our 58 patient study population was smaller than originally planned because an additional 42 subjects at a third site were disqualified after many received other new treatments during the study. Clinical records from this site did not permit us to identify which patients were so treated and to maintain them in an intent-to- treat analysis, as the protocol stipulated. Because each site was randomized separately, however, this exclusion did not alter the active: placebo device ratio, permitting us to analyze the remaining two site population in this manner. While we recognize this exclusion as a departure from the protocol, we believe it to be an appropriate approach to this unusual occurrence.

The significance of the results in spite of this unforeseen reduction is explained primarily by the large effect size of active treatment, but also by both the severity of baseline disease and symptoms and the low response to placebo treatment. Semiflexed knee X-rays showed Kellgren–Lawrence Grade 3 changes in 52% of patients and Grade 4 changes in 48%, and WOMAC pain scores were greater than 200 in 74% of active and 63% of placebo patients in spite of baseline NSAID and/or analgesic therapy. Placebo patients experienced low frequencies of 50% or greater improvement in outcome measures in contrast to a higher proportion of the actively treated patients. The lower than expected patient numbers, the lower than recommended total treatment hours in 40% of study patients, and the relatively brief study duration probably all contribute to the one primary and two secondary outcomes that did not reach significance, suggesting that even greater effectiveness would be demonstrated in the absence of these limitations, as suggested by another published cohort study[10]. PES therapy was added to current, stable, and continuous background OA drug treatment. No ''wash out'' of OA medicines was conducted to produce a flare in baseline symptoms. Thus the finding of increased efficacy on top of background therapy also emphasizes the clinical significance of the results.

These data confirm and extend the results of previous studies using the same PES signal, including a 1-month randomized, placebo-controlled trial[7], a long-term TKA deferral study[8,9], and clinical experience captured in a phase IV treatment cohort[10]. Other investigators have also improved knee OA symptoms with a different highly specific PES signal[27–29]. In contrast, another recent trial using an electronically and biophysically different pulsed electromagnetic field (PEMF) device failed to provide relief for 90 knee OA patients[30]. These differing results indicate that the efficacy of PES resides in the specific properties of the electrical signal generated by each device type, that the signal must be optimized and proven in clinical trials to assure

Table II(c)
Absolute difference from baseline in millimeters

	Active ($N=39$)		Placebo ($N=19$)		Active–Placebo ($N=58$)		
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	*P* value
Patient global	12.9	24.45	−3.7	23.43	16.6	24.13	0.017
Patient pain	14.7	23.12	2.3	21.95	12.4	22.75	0.057
WOMAC pain	13.2	22.33	3.1	15.38	10.1	20.35	0.080
WOMAC stiffness	15.4	23.55	3.3	18.29	12.1	22.00	0.053
WOMAC function	12.0	19.22	−1.7	13.48	13.7	17.58	0.007
Total WOMAC	12.5	19.34	−0.3	12.43	12.8	17.42	0.004

Table II(d)
Percent change from baseline

	Active ($N=39$)		Placebo ($N=19$)		Active−Placebo ($N=58$)		
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	*P* value
Patient global	24.2	47.87	−26.3	90.43	50.6	64.68	0.032
Patient pain	30.3	46.28	−0.9	63.74	31.2	52.53	0.038
WOMAC pain	25.1	45.57	5.3	39.46	19.9	43.70	0.110
WOMAC stiffness	26.3	41.15	1.2	38.39	25.1	40.29	0.030
WOMAC function	24.2	41.71	−5.3	39.31	29.5	40.95	0.013
Total WOMAC	25.6	39.05	−1.1	33.42	26.7	37.34	0.014

efficacy, and that positive or negative treatment outcomes obtained with one signal cannot be extrapolated to different signals.

The mechanism of action by which this specific PES device relieves joint symptoms in *human* knee OA is not known yet, but three decades of *in vitro* and animal research provide compelling evidence for a positive local effect on chondrocyte function through gene regulation. *In vitro* studies of cartilage explants have demonstrated that specific, pulsed electrical signals stimulate synthesis of DNA, Type II collagen, and aggrecan, while simultaneously inhibiting production of molecules that destroy cartilage such as matrix metalloproteinases and interleukin-1[11–22]. A recent article confirmed very substantial 500−800% upregulation of chondrocyte Type II collagen and aggrecan genes in response to a capacitively coupled signal[22]. These changes in gene expression are mediated through intracellular signal transduction cascades that increase intracellular calcium concentration from cytoplasmic stores. These biological changes are analogous to the gene regulating effects of hormones, growth factors, and chemical ligands[31]. Parallel results have been observed with specific PES of other mesenchymal cell types, including osteoblasts and fibroblasts[32–34].

In animal studies, Lippiello and coworkers measured the physical characteristics of natural electrical fields generated by articular cartilage and designed a device to deliver this pulsed electrical signal to knee cartilage from surface electrodes applied over the knee. In a rabbit model of OA, this device altered repair of injured cartilage to regenerate hyaline cartilage instead of typical scar tissue and fibrocartilage[35]. This positive effect needs to be studied in humans with acute cartilage injury. What emerges from this body of evidence is an essential role of intrinsic electrical signaling in cartilage health and disease and the opportunity to treat diseases of cartilage with optimized, capacitively coupled PES devices.

Some critics have suggested that PES devices relieve symptoms in the same manner as TENS. This is unfounded. In fact, TENS and PES differ in many ways. TENS stimulates nerves; the device used in this trial does not. Optimal pain relief from TENS requires its application two to four times daily for a usual maximum of 40 min; longer use attenuates pain relief. The PES device is used for 6−14 h each day, and other studies show that greater use results in greater efficacy[10]. TENS causes rapid release of enkephalins and endorphins; pain relief occurs in minutes and wanes in a few hours, just as with opiates[24]. PES requires weeks to months of treatment for optimal pain relief, but then the effect usually persists for weeks to years after treatment withdrawal. Tolerance develops with TENS but not with PES.

Knee OA causes severe disability in millions of people. Those with moderate or severe disease who fail analgesics and/or NSAIDs have limited therapeutic options. Some choose TKA or other types of surgery, but many are unwilling or are too young, too old, or too enfeebled by co-morbid disease to consider surgery. PES offers a safe, noninvasive option for such patients, and may reduce the need for TKA as well.

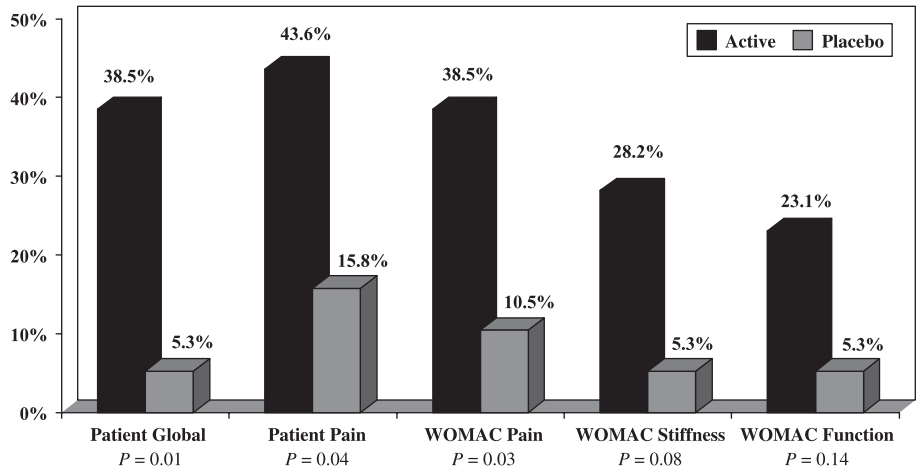

Fig. 2. Percentage of patients improving 50% or greater in each of the primary outcome measures.

Table III
The hours of use of the device in the two treatment groups and the percentage of patients who were compliant with the requirement to use the device for a minimum average of 6 h/day. Use was measured by a timer incorporated into the device. There were no statistically meaningful differences between the two treatment groups

Hours used	Mean	Standard deviation	Range
Placebo	656.4	193.2	310–1052
Active	691.6	187.2	00.00–1019.1
Compliance	Percent		
Placebo	63.1		
Active	65.8		

Acknowledgment

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