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Original Papers

Effects of Noninvasive Interactive Neurostimulation on Symptoms of Osteoarthritis of the Knee: A Randomized, Sham-Controlled Pilot Study

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Abstract

Objective: To explore the effects of noninvasive interactive neurostimulation used as an adjunct to usual care, on pain and other symptoms in adults with osteoarthritis of the knee.
Design: Randomized, sham-controlled trial.
Setting: A university in the southern United States.
Subjects: Thirty-seven (37) adults with knee osteoarthritis (based on American College of Rheumatology diagnostic criteria).
Interventions: Seventeen (17) noninvasive interactive neurostimulation (active or sham) sessions over 8 weeks with a week 12 follow-up.
Outcome measures: Eleven-point numeric rating scale for weekly pain; Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), patient global assessment, and Short-Form Health Survey (SF-36) completed at baseline and weeks 4, 8, and 12.
Results: For the main outcome, pain, the differences between the groups over time did not reach statistical significance (all $p > 0.05$). However, a clinically important reduction in pain (defined as a 2-point or 30% reduction on an 11-point numeric rating scale) was maintained at week 12 by the active noninvasive interactive neurostimulation group (2.17 points, 34.55% reduction) but not the sham group (1.63, 26.04% reduction). Pain improved over time in participants regardless of group membership (numeric rating scale average pain, $p = 0.002$; numeric rating scale worst pain, $p < 0.001$; and WOMAC pain, $p < 0.001$), as did WOMAC function, WOMAC stiffness, and WOMAC total score (all $p < 0.001$). Repeated measures ANOVA revealed a statistically significant difference between the groups over time for the SF-36 Vitality scale, $F\ (3, 105) = 3.54$, $p = 0.017$. In addition, the active device group improved on the patient global assessment from baseline to week 8 compared to the sham device group, $F\ (1, 35) = 4.025$, $p = 0.053$.
Conclusions: In this pilot study, clinically important reductions in knee pain were maintained at week 12 in the active, but not the sham, noninvasive interactive neurostimulation group. Further study of this noninvasive therapy is warranted.

Introduction

Arthritis is the leading cause of disability among adults in the United States, affecting almost 6 out of 10 adults aged 65 or older.[1] Osteoarthritis (OA), the most common form of arthritis,[2] is the eighth leading cause of disability globally.[3] The knee is the joint most frequently associated with disability.[4]

No cure for OA currently exists. Treatment is focused on managing the pain and dysfunction associated with the disease. American College of Rheumatology (ACR) guidelines for the medical management of knee OA recommend nonpharmacologic modalities as the first line of treatment.[5] The current study explored the effects of noninvasive interactive neurostimulation (NIN) on OA of the knee.

The hand-held, 9V battery-powered NIN device (InterX5000, Neuro Resource Group, Plano, TX) is based on technology originally developed in Russia. This device has not yet been well studied in randomized, controlled trials in the United States. While unpublished clinical evidence sug-

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gests that NIN would be an effective treatment for OA of the knee, a search of Medline (1966–April 2006) and CINAHL (1982–2005) uncovered no trials of the device used in this study. However, there is some evidence indicating that another approach to delivering electrical stimulation, transcutaneous electric nerve stimulation (TENS), can play a role in the treatment of pain associated with OA of the knee.[6–10] There is also some evidence supporting the use of acupuncture in the treatment of knee OA.[11] NIN therapy is related to acupuncture in that the device is used directly on acupuncture points and is thought to act on the energetic system of the body. Acupuncture points, according to classical acupuncture theory, are points at which the vital energy (*qi*) can be accessed and rebalanced. Rebalancing the flow of *qi* restores harmony to the system.[12] In the Western medical model, acupuncture is thought to relieve pain through the gate-control mechanism or through the release of neurochemicals.[13,14]

Although their mechanism of action is unclear, both NIN therapy and TENS are hypothesized to work through one or both of these mechanisms as well.[15–18] The NIN device generates high amplitude nondamaging current impulses that stimulate C fibers and A-delta fibers thought to release neuropeptides into the bloodstream, promoting healing and inducing analgesia.

Unlike other forms of electrical stimulation commonly used in the U.S., the NIN device senses changes in the skin's resistance, and adjusts the impulses it sends in response, thereby providing the optimal stimulus throughout the treatment session.[19] In addition, the device identifies key low impedance points related to the condition and requiring treatment.[19] This diagnostic feedback regarding skin impedance informs the therapist which areas to treat and when treatment of a location is complete.[20] The interactive nature of this more recently developed electrical stimulation device may improve upon the effectiveness of conventional TENS.

The purpose of the current study was to explore the effects of adjunctive NIN on participants with OA of the knee. Based on studies that had used TENS or acupuncture, the investigators hypothesized that 8 weeks of NIN therapy, used as an adjunct to usual care, would reduce knee pain, dysfunction, and stiffness, reduce the impact of the condition on overall wellbeing, and improve health-related quality of life in participants with OA of the knee when compared to sham therapy.

Materials and Methods

Participants

Potential participants were informed of this Institutional Review Board–approved study by newspaper advertisements, brochures, and study flyers posted in physician offices and public places in central Virginia. Interested individuals contacted the study coordinator, who assessed their eligibility to participate based on the following inclusion criteria: 50 years of age or older; physician confirmed diagnosis of OA of the knee (based on ACR diagnostic criteria); knee pain of at least 6 months duration; moderate or greater knee pain severity (defined as a score of 3 or greater on an 11-point numeric pain rating scale) for most days in the past month; and willingness to abide by protocol and treatment schedule.

In addition, potential participants were asked to maintain stable use of any supplements or medications they were already taking and commit to avoiding use of any new drugs or treatments for their knee pain during the study period.

Persons were excluded if they had: electrical implants; corticosteroid or hyaluronic acid injection into the knee within the previous 3 months; significant injury to the knee within the past 6 months; arthroscopy of the knee within the past year; joint replacement of the involved knee; uncontrolled concomitant disease affecting the knee, such as rheumatoid arthritis; use of assistive devices other than a cane or knee brace; or disease of the spine or other lower extremity joints of sufficient degree to affect assessment of the knee.

From March 2005 through April 2006, eligible participants provided informed consent and were randomly assigned to either the active or sham NIN device group using a block randomization schedule, blocked in groups of 6. The allocation sequence was generated using a random number table. A statistician provided sequentially numbered opaque envelopes that contained the group assignment. The therapist opened the next envelope in sequence just prior to administering the intervention.

Because no studies have used the NIN device with OA, sample size estimates were based on mean differences in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale scores in a study that compared acupuncture to standard care.[21] Power analysis revealed that to achieve a power (group by time) of 80% with an alpha of 0.05, a total sample of 24 participants would be required to determine a significant change in WOMAC pain scores. This was based on a mean difference between baseline (9.6 ± 3.3) and week 8 (5.3 ± 3.6) of 4.3 points on the Likert version of the WOMAC for the active group, but only a 0.3 point difference between baseline (9.8 ± 2.8) and week 8 (9.5 ± 3.6) for the control group. In an effort to be more conservative, a larger required sample size of 30 was set as the goal for this study. To allow for a 33% loss to follow-up, 40 participants were assigned to either the sham ($n = 20$) or the active ($n = 20$) device group.

Instruments

The WOMAC, a 24-item, self-administered, condition-specific questionnaire, was used to measure pain, dysfunction, and stiffness at each time point. The WOMAC is a reliable, valid, responsive instrument[22–26] that has been recommended by the Outcome Measures in Rheumatology Trials (OMERACT) guidelines as an outcome measure for clinical trials of OA of the hip or knee.[27] We used the 11-point numeric rating scale version of the questionnaire.

Participants also rated their pain (current, average, least, and worst) one evening a week at home using an 11-point numeric rating scale (NRS) with the anchors 0 "no pain" and 10 "worst pain possible." This type of scale has demonstrated validity and reliability.[28–31] In a clinical trial, a 2-point or 30% reduction is considered a clinically important difference on an 11-point NRS pain intensity measure.[32,33] In this study, a score below 3.23 was also considered clinically important. On a 0 to 100 mm VAS scale, patients consider themselves well at scores below 32.3 mm, which is the patient-acceptable symptom state for pain associated with knee OA.[34]

Patient Global Assessment was measured using an 11-point numeric rating scale (0 being "as well as possible" and 10 being "as bad as possible") for this instruction: "Considering all the ways your knee arthritis affects you, circle the number that best describes how well you have been doing over the last month." This is a recommended way to assess this outcome.[24]

The self-administered Short-Form Health Survey (SF-36) was used to assess health-related quality of life. This reliable and valid instrument[35–39] is the most commonly used generic measure of perceived health in the orthopedic literature.[40]

The NRS pain scales (current, average, least, and worst) were collected weekly; all other measures were completed at baseline, week 4, week 8, and week 12 follow-up (4 weeks after the last NIN session). In addition, at week 8 participants indicated which device they thought had been used on them by checking one of the following response options: active, sham, or don't know.

Intervention

In addition to continuing with their usual care, participants received 20 to 30 minute NIN treatments for 8 weeks on the following schedule: three times a week for weeks 1 through 3, two times a week for weeks 4 through 6, and once a week for weeks 7 and 8. Each treatment (active or sham) was administered according to a manualized protocol that specified how and where the device was to be used for each particular session. During a treatment session, the device was applied to the knees, back, dermatomes, or acupuncture points (ST 35, GB 34, SP 9, BL 40, or LI 4) and held stationary or moved along the skin in sweeping motions based on the protocol. Two study therapists had been trained by an expert in NIN therapy to ensure proper use of the device.

When using the active device, the therapist measured relative impedance of the skin to determine optimal treatment sites within the area specified by the protocol. Because it was not possible to obtain a sham device that retained the diagnostic function while disabling the therapeutic stimulus, the study therapists could not be blinded to group assignment. However, the sham NIN device looked identical to the active device and made similar sounds, so participants would not know which device was being used on them.

Data analysis

Data were analyzed using SPSS for Windows, v.14.0.2. Using chi-square tests for categorical and independent *t*-tests for continuous variables, baseline data were analyzed to determine whether or not there were any significant differences between treatment groups. Separate repeated measures analysis of variance (ANOVA) models were used to determine changes in pain and other outcomes over time (time main effect), and to determine whether or not these changes over time differed between the active and sham device groups (interaction of group by time). Assumptions of normality, homogeneity of variance, additivity, and sphericity were assessed using the Shapiro-Wilk, Levene, Tukey, and Mauchly tests, respectively. When the assumption of sphericity was not met, the conservative Greenhouse-Geisser epsilon correction was used to assess the statistical significance or within-subjects effects. Statistically significant group by time interactions were further explored using contrasts. Significant main effects for time were followed by dependent *t*-tests across time points. Because this was an exploratory study, the significance level of 0.05 was used for all tests, and trends were examined. The percent change was explored for statistically significant differences between time points. This was calculated as follows: [(final value – initial value)/initial value] $\times$ 100.

Missing values in this analysis were replaced with the mean of the subscale as per the WOMAC and SF-36 instructions. The conservative last value carried forward method was used to impute missing data on the patient global assessment and NRS pain scales.

Results

A total of 37 participants completed the study. Twenty-five (25) of the 37 participants were female (68%), 12 were male (32%). Thirty-six (36) participants were white (97%), one was African-American (3%). Participants ranged from 50 to 91 years of age, mean 67.46 $\pm$ 10.36 years. The number of years since their diagnosis ranged from 0 to 24, mean 7.54 $\pm$ 6.29 years. The mean body mass index (BMI) was 30.51 $\pm$ 5.52, with a range of 19.49 to 43.93. There were no statistically significant differences on any demographic or baseline study variables between the active ($n = 18$) and sham ($n = 19$) device groups ($p > 0.05$ for all) (Table 1).

Effects of NIN therapy

Although the differences between the groups over time for the main outcome, pain, did not reach statistical significance on any of the pain measures ($p > 0.05$ for all), there were clinically important reductions in pain (defined as a 2-point or 30% reduction on an 11-point NRS). From baseline to week 4, average pain NRS scores decreased 3.06 points (48.73%) in the active group versus 2.00 points (31.95%) in the sham device group (Table 2). From week 4 to week 8, as the treatment frequency decreased, pain in the active group increased by 0.34 points while sham NIN group pain continued to diminish slightly (–0.21 points). By week 12 (4 weeks after the last treatment session), pain ratings for both groups were climbing from week 8 levels. The total reduction from baseline to week 12 was a clinically important 2.17 points (34.55%) in the active group versus 1.63 points (26.04%) in the sham NIN group.

No clinically important pain reductions or statistically significant differences between the groups over time were noted on the worst pain NRS scores ($p > 0.05$). WOMAC pain scores decreased most from baseline to week 4, continued to decrease to week 8 (less so in the active than in the sham NIN group), then increased slightly in the active group while continuing to decrease in the sham device group post-intervention (Table 3). A similar pattern was seen with the other WOMAC scores. Although not statistically significant ($p > 0.05$ for all), the active group improved more than the sham device group when the treatments were most frequent. Once treatment frequency decreased, the sham group continued to improve, while little additional improvement was noted in the active group on the function and total score, and stiffness actually increased from week 4 to week 8.

Table 1. Baseline Demographics

	Active (n = *18*)	*Sham* (n = *19*)	t-*test*	p
Sex				
Male	5 (27.78%)	7 (36.84%)		
Female	13 (72.22%)	12 (63.16%)		
Race				
White	18 (100.00%)	18 (94.74%)		
African-American	0	1 (5.26%)		
Age	70.11 ± 10.27	64.95 ± 10.06	−1.54	0.13
Years since diagnosis	7.50 ± 7.41	7.58 ± 5.22	0.04	0.97
BMI	29.25 ± 5.67	31.70 ± 5.25	1.36	0.18
NRS average pain score	6.28 ± 1.78	6.26 ± 1.56	−0.03	0.98
WOMAC pain score	25.44 ± 9.61	27.05 ± 10.54	0.48	0.63
WOMAC function score	88.33 ± 38.28	86.95 ± 30.32	−0.12	0.90
WOMAC stiffness score	11.83 ± 4.20	13.47 ± 4.23	1.18	0.25
WOMAC total score	125.61 ± 50.45	127.47 ± 41.92	0.12	0.90
Patient global assessment score	5.72 ± 1.96	5.37 ± 1.71	−0.59	0.56
SF-36 physical functioning	37.22 ± 23.53	42.37 ± 14.94	0.79	0.44
SF-36 role physical	37.50 ± 33.49	30.26 ± 33.93	−0.65	0.52
SF-36 general health	63.11 ± 14.55	69.32 ± 22.48	1.00	0.32
SF-36 vitality	50.83 ± 18.17	58.95 ± 20.99	1.25	0.22
SF-36 social functioning	72.22 ± 24.84	78.29 ± 19.91	0.82	0.42
SF-36 role emotional	85.19 ± 26.13	77.19 ± 38.57	−0.73	0.47
SF-36 bodily pain	41.33 ± 15.50	39.68 ± 10.03	−0.38	0.71
SF-36 mental health	82.22 ± 10.65	81.89 ± 13.94	−0.08	0.94

BMI, body–mass index; NRS, numeric rating scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; SF-36; Short Form–36.

When considering the total sample (ignoring group membership), there were statistically significant improvements over time in the following pain measures: average pain NRS, F (4.227, 147.948) = 4.316, $p = 0.002$; worst pain NRS, F (5.228, 182.988) = 5.644, $p < 0.001$; and WOMAC pain scores, F (2.214, 77.487) = 21.693, $p < 0.001$; as well as the WOMAC function subscale, F (2.339, 81.876) = 25.118, $p < 0.001$; WOMAC stiffness subscale, F (3, 105) = 17.883, $p < 0.001$; and WOMAC total score, F (2.329, 81.508) = 25.841, $p < 0.001$.

A statistically significant difference between the groups over time was found for the SF-36 Vitality scale, F (3, 105) = 3.54, $p = 0.017$. Specific contrasts revealed significant differences from baseline to week 8, F (1, 35) = 5.433, $p = 0.026$ with vitality increasing in the active device group, while sham device group scores decreased. Statistically significant differences between the groups over time were not found on any of the other SF-36 subscales ($p > 0.05$ for all).

Repeated measures ANOVA across all time points did not show a statistically significant difference between the groups over time on the Patient Global Assessment, F (3, 105) = 2.308, $p = 0.081$. However, from baseline to week 8, the active group improved by 2.61 points (46%) while the sham improved by 1.05 points (20%); the simple contrast for these two time points indicated a strong trend, F (1, 35) = 4.025, $p = 0.053$. At week 12, 4 weeks after the last NIN session, slight deterioration in the Patient Global Assessment score was apparent in the active group, while the sham group score indicated continued improvement.

At the end of the intervention, 20 of the 37 participants (54%) reported that they did not know which device had been used on them. Two participants thought they were in the sham group, 14 thought they had been treated with the active device. One active device group participant reported that he thought he had been treated with both devices. There were no serious adverse events associated with the use of either device.

Discussion

In this study, NIN therapy resulted in clinically important reductions in pain; however, differences over time between the active and sham device groups did not reach statistical significance. While both groups experienced clinically important pain reductions at weeks 4 and 8 (as measured by NRS), by week 12 only the active device group maintained a clinically important 35% reduction in pain compared to baseline. While analyzing the data, two possible explanations as to why the results may have been clinically important yet failed to reach statistical significance became apparent: the treatment frequency may have been suboptimal, and the study was underpowered.

The first explanation relates to the frequency of treatments. Through week 4, there were 11 treatment sessions. From weeks 5 through 8, there were only 6 sessions. From baseline to week 4, when treatment sessions were the most frequent, the active NIN group achieved a mean NRS pain score at which patients with knee OA consider themselves well; however, this acceptable level of pain was not maintained when treatment frequency was reduced. Also, on the WOMAC scales, the active device group improved more than the sham group when the treatment sessions were most frequent. But this advantage was lost when the treatment frequency was reduced: then the sham device group improved more than the active. These results suggest that the treatment frequency may have been reduced too soon to provide

Table 2. Changes from Baseline in 11-Point Numeric Rating Scale (NRS) Average and Worst Pain Scores

Outcome	*Baseline*[a]	*Week 1*	*% change*	*Week 4*	*% change*	*Week 8*	*% change*	*Week 12*	*% change*
NRS average pain									
Active	6.28 ± 1.78	4.72 ± 1.64	−24.84%	3.22 ± 2.26	−48.73%	3.56 ± 2.01	−43.31%	4.11 ± 2.35	−34.55%
Sham	6.26 ± 1.56	5.26 ± 1.66	−15.97%	4.26 ± 1.33	−31.95%	4.05 ± 1.84	−35.30%	4.63 ± 1.83	−26.04%
Total sample	6.27 ± 1.64	5.00 ± 1.65	−20.26%	3.76 ± 1.89	−40.03%	3.81 ± 1.91	−39.23%	4.38 ± 2.09	−30.14%
NRS worst pain									
Active		6.61 ± 1.50		4.67 ± 2.64	−29.35%	5.28 ± 2.76	−20.12%	5.28 ± 2.78	−20.12%
Sham		7.21 ± 1.62		5.84 ± 1.61	−19.00%	5.63 ± 2.48	−21.91%	5.79 ± 2.20	−19.69%
Total sample		6.92 ± 1.57		5.24 ± 2.23	−24.28%	5.46 ± 2.59	−21.10%	5.54 ± 2.48	−19.94%

[a]Worst pain was not measured at baseline.

Table 3. Changes from Baseline in WOMAC Scales, Patient Global Assessment, and SF-36 Vitality

Outcome (score range)	*Baseline*	*Week 4*	*% change*	*Week 8*	*% change*	*Week 12*	*% change*
WOMAC pain (0–50)[a]							
Active	25.44 ± 9.61	15.33 ± 10.99	−40%	13.67 ± 9.88	−46%	14.17 ± 10.68	−44%
Sham	27.05 ± 10.54	19.63 ± 9.09	−27%	16.16 ± 10.19	−40%	15.89 ± 8.92	−41%
WOMAC function (0–170)[a]							
Active	88.33 ± 38.28	53.33 ± 34.58	−40%	46.62 ± 31.32	−47%	48.17 ± 35.63	−45%
Sham	86.95 ± 30.32	66.00 ± 30.15	−24%	52.37 ± 29.10	−40%	57.81 ± 29.65	−34%
WOMAC stiffness (0–20)[a]							
Active	11.83 ± 4.20	7.50 ± 4.19	−37%	8.00 ± 4.39	−32%	8.06 ± 4.15	−32%
Sham	13.47 ± 4.23	9.89 ± 5.07	−27%	8.32 ± 4.50	−38%	8.37 ± 4.18	−38%
WOMAC total (0–240)[a]							
Active	125.61 ± 50.45	76.17 ± 47.35	−39%	68.29 ± 43.00	−46%	70.39 ± 48.82	−44%
Sham	127.47 ± 41.92	95.52 ± 41.93	−25%	76.84 ± 41.60	−40%	82.07 ± 39.70	−36%
Patient global assessment (0–10)[a]							
Active	5.72 ± 1.96	3.61 ± 2.25	−37%	3.11 ± 1.78	−46%	4.11 ± 2.37	−28%
Sham	5.37 ± 1.71	4.63 ± 1.57	−14%	4.32 ± 1.83	−20%	4.21 ± 1.51	−22%
SF-36 vitality subscale (0–100)							
Active	50.83 ± 18.17	55.56 ± 21.62		59.72 ± 17.78		55.28 ± 19.74	
Sham	58.95 ± 20.99	60.26 ± 18.14		56.58 ± 21.73		64.47 ± 17.39	

[a]Lower scores are better on these measures.
WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index; SF-36, Short Form–36.

the optimal symptom improvement achievable by the therapy. Providing more treatment sessions for a longer period of time may be required to achieve statistically significant reductions in pain and dysfunction.

The second explanation has to do with inadequate statistical power. The sample size in this pilot study was small, which led to low power in the pain and WOMAC measures. The 46% reduction in pain in the active device group as measured by the WOMAC at week 8 compares favorably with two larger acupuncture studies; however, the 40% reduction in pain for the sham device group in the current study was greater than that experienced by the control groups in those studies.[21,41] With such a large effect for the sham group in the current study, even a 46% pain reduction in the active group failed to produce a statistically significant interaction effect (power = 0.097). A much larger sample size would have been necessary to determine whether the difference between the groups across time was significant.

The changes on the WOMAC function subscale (47%) and total score (46%) in the active NIN device group were also similar to those reported in acupuncture studies that resulted in statistically significant differences between the groups over time.[21,41,42] In addition, the Patient Global Assessment findings tended to indicate that the active device group had improved more than the sham device group at the end of the treatment period. These findings lead the authors to believe that a better powered study of the NIN device is worth considering.

Recommendations for future studies include increasing the sample size and planning a more intensive treatment schedule. The manufacturer has developed a device designed to be used by individuals at home. Thus, it would be feasible for participants to use the device on themselves at home 3 to 5 times a week over a longer period of time. Use of the home device would remove the therapist from the equation, effectively reducing the potential placebo effect due to the therapist/participant interaction that occurred in the present study, addressing this concern as well.

Conclusions

Adjunctive NIN therapy was not shown to be statistically superior to sham therapy in reducing knee pain in participants with osteoarthritis of the knee; however, clinically important reductions in knee pain were maintained at week 12 in the active, but not the sham, NIN group. Statistically significant improvements were found in the active device group compared to the sham device group in the SF-36 subscale of vitality. In addition, a trend was noted for the active NIN group in improvement on the patient global assessment from baseline to week 8 compared to the sham NIN group. Given the clinically important pain reduction found in this pilot study, further study of this noninvasive device is warranted.

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Disclosure Statement

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