Prospective Randomized Single-blinded Controlled Clinical Trial of Percutaneous Neuromodulation Pain Therapy Device Versus Sham for the Osteoarthritic Knee: A Pilot Study

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This pilot study presents the initial results for a percutaneous neuromodulation pain therapy device (Deepwave) that is associated with no morbidity, good pain relief, and increased function in patients with knee osteoarthritis.

Osteoarthritic pain can be debilitating and lead to significant and undesirable lifestyle changes. Increased emphasis on addressing pain has been fueled by the recent description of pain as the "5th vital sign" by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO).[1] Despite efforts to develop new technologies and methods to treat pain, an "analgesic gap" exists.[2,3]

Currently, the first step in symptomatic relief includes anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase (COX)-selective drugs in conjunction with lifestyle modifications. Often, these measures are not sufficient to completely alleviate the pain, which pushes patients to seek other alternatives such as depot corticosteroid injections, narcotics, and surgery. However, narcotics are capable of producing adverse effects including respiratory depression, sedation, nausea, vomiting, and even behavioral problems.[4] Corticosteroid injections are more invasive, can only be repeated on a limited basis (ie, up to 3 times each year), and have an associated risk of infection and post-steroid flare-up.[5] For these reasons, other treatment methods are needed to help close the treatment gap and thus reduce patient morbidity.

In addition to pharmacologic treatments, other nonpharmacologic alternatives have been used including acupuncture, cooling, physical therapy, chiropractic manipulation, and transcutaneous electrical nerve stimulation. Unfortunately, these alternatives fall short with respect to duration and magnitude of analgesia.

Transcutaneous electrical nerve stimulation has been used for 3 decades in a variety of situations to relieve pain.

Transcutaneous electrical nerve stimulation has been used for 3 decades in a variety of situations to relieve pain.[6-14] Using transcutaneous electrical nerve stimulation is justified by the gate control theory, which states that the brain recognizes a limited amount of neural input from a given point in the body at any given moment. This impulse may be superseded by another more powerful and conducive neural input. Although transcutaneous electrical nerve stimulation has been shown to be useful for superficial tissues, it lacks the ability to penetrate into deeper tissue.

A recently developed deep tissue percutaneous neuromodulation pain therapy device, Deepwave (Biowave Corp, Norwalk, Conn), is a viable alternative for narrowing the analgesic gap in treating osteo-

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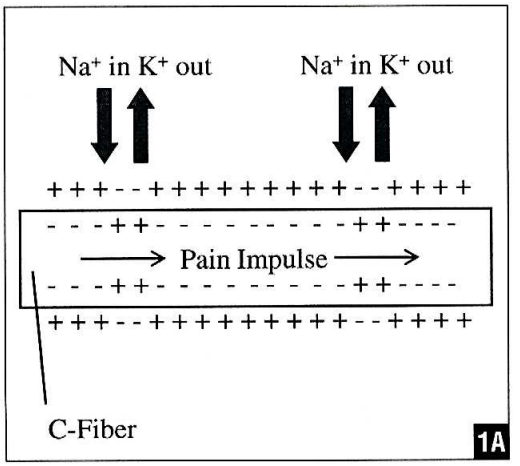

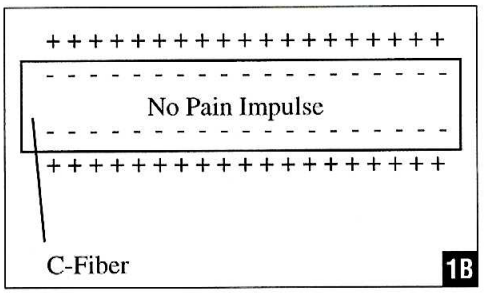

Figure 1: Deepwave (Biowave Corporation, Norwalk, Conn) mechanism of action via frequency conduction block. Normal propagation of pain signal along pain fibers (C-fibers) (A). Deepwave electric field interrupts sodium/potassium ion exchange, thereby inhibiting the cell wall from changing polarity and impeding transmission of pain impulses (B).

arthritic pain. Unlike transcutaneous electrical nerve stimulation, the Deepwave device can deliver a precise electrical signal to a specific volume of tissue in the body that blocks the transmission of pain impulses. The electrical signal created in the body is theorized to have a secondary effect of releasing endorphins and serotonin, and therefore leading to a localized analgesia at the treatment site. This analgesic effect depends on the duration and amplitude of treatment.

The Deepwave device sends a premixed modulated envelope of two high frequency electronic wave forms ("feed signals") into deep tissue via a larger feed electrode and a smaller pain site electrode called a percutaneous electrode array. The percutaneous electrode array facilitates delivery of the feed signals into deep tissue by providing a direct conductive pathway for current through the outermost layers of skin.

Percutaneous electrode arrays are comprised of 1014 microneedles, each of which is 0.73 mm in length and housed within a 2.5-inch diameter hydrogel-based electrode. Polarized structures in the body cause an electric field to form with a low frequency component equal to the difference in frequency between the two feed signals. Formation of the low frequency field occurs in the form of a modulated electric field envelope with a location dependent on the placement of the two electrodes. The volume of tissue affected is dependent on electrode size and placement as well as the amplitude of the feed signals. With the configuration used in this study, the electric field is believed to form immediately adjacent to and beneath the percutaneous electrode array over the pain site, along the path between the opposing feed electrode and the percutaneous electrode array. The low frequency electric field is believed to demodulate nerve cells, resulting in an altered Na+/K+ equilibrium. As a result, the membrane potential of the nerve cell is stabilized (hyperpolarized) and is therefore unable to transmit action potentials and thereby pain impulses (Figures 1 and 2).

The use of Deepwave as a single therapy is efficacious and safe in reducing the severity of acute and chronic pain in knee osteoarthritis patients. This study investigated the efficacy of Deepwave in reducing knee pain experienced by our patient population, and reduction of drug consumption over the 1-week period following the treatment.

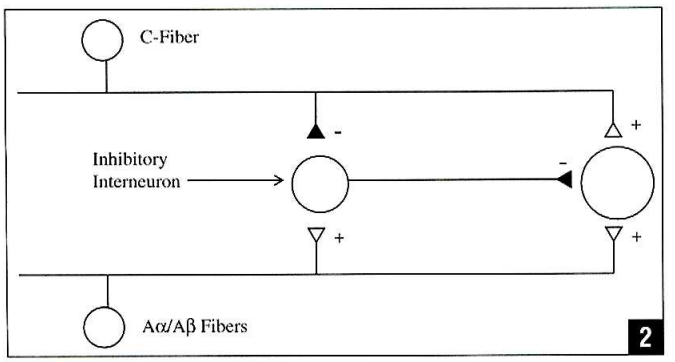

Figure 2: Deepwave (Biowave Corporation, Norwalk, Conn) mechanism of action via the gate control theory. The Deepwave may also activate the Aα/Aβ fiber, which occurs at both the inhibitory interneuron and projection fiber, thus causing a suppression of the pain sensation.

Materials and Methods

Patients

This is an Institutional Review Board-approved, single-blinded, randomized pilot study of 70 patients over an 8-month period. The study began in March 2005 and the data from the last patient was collected in December 2005. Patients were blinded to either live or sham treatment groups. All patients presented to the clinic with knee pain secondary to osteoarthritis. The diagnosis of knee osteoarthritis was made based on the American College of Rheumatology guidelines, which include knee pain with radiographic changes of osteophyte formation and at least one of the following: patient age >50 years, morning stiffness lasting ≤30 minutes, or crepitus on motion.[15] Informed consent was received on 70 patients. Seven patients were lost to follow-up. Of the 63 completed patients, 28 patients were randomly assigned to the sham group and 35 patients were randomly assigned to the live treatment group. Table 1 presents the demographics for these two groups.

Inclusion criteria consisted of any man or woman who met the following conditions: aged between 18-85 years, diagnosis of osteoarthritis, knee pain secondary to osteoarthritis with a visual analog pain scale

Table 1

Patient Demographics for Live and Sham Groups

	No (%)	
	Live Treatment (N=35)	**Sham Treatment (N=28)**
Men	11	7
Women	24	21
Mean age (range)	55.3 (34-83)	58.2 (28-80)
Affected side		
Right	15 (43)	10 (36)
Left	20 (57)	18 (64)
Pain location		
Anterior	33 (94)	25 (89)
Posterior	6 (17)	7 (25)
Medial	18 (51)	12 (43)
Lateral	7 (20)	5 (18)

Table 2

Comfort and Safety Profile of Live and Sham Groups at 1-week Follow-up

	No (%)		
	Live	**Sham**	***P* value**
Comfortable			.872
Yes	34 (97)	27 (96)	
No	1 (3)	1 (4)	
Pain/pressure/tingling			.367
Yes	1 (3)	2(7)	
No	34 (97)	26 (93)	
Skin adverse effects			.427
Yes	1 (3)	0 (0)	
No	34 (97)	28 (100)	

>30 mm, and the ability to understand and willingness to cooperate with the study procedures.

Exclusion criteria excluded any patient with an allergy or intolerance to adhesive materials; surgical intervention or injection of a corticosteroid or viscosupplement within the prior 30 days of the treatment of the painful knee or its underlying etiology; history of any substance abuse or dependence within the past 6 months; history of pacemaker use; existence of implantable electronic devices; any clinical evidence of cardiovascular, pulmonary, renal, psychological, hepatic, neurological, hematologic or endocrine abnormalities; and having received an investigational drug or device in the past 30 days.

Pain Therapy Device

The Biowave deep tissue neuromodulation pain therapy device (Deepwave) was used. The active percutaneous electrode placed over the pain site was a 1.5-inch diameter round percutaneous electrode array embedded within a 2.5-inch diameter round carbon/silver electrode (Unipatch, Wabash, Minn). The feed electrode placed opposite the pain site was the Classic 2404, 4×2-inch self adhesive electrode (Unipatch).

Visual Analog Pain Scale

A visual analog pain scale was used to determine pre- and post-treatment pain levels (immediate, 6 hours, 24 hours, and 48 hours post-treatment). A 100-mm scale was used to mark the patient's subjective pain. At the far left of the scale was "no pain" and on the far right was "worst pain imaginable." The visual analog pain scale has been proven to be a valid and reliable assessment of pain.[16]

Treatment

For all patients, the active percutaneous electrode was positioned on their site of maximum knee pain while the feed electrode was placed directly across the joint line (medial and lateral or anterior and posterior). Treatment duration was 30 minutes in both groups. Patients were instructed to sit in a chair with their backs to the Biowave machine. Live treatment group patients were instructed to tell the examiner when they had achieved the highest tolerable intensity. The intensity levels then were reassessed and increased as tolerated by the patient after 5, 10, and 15 minutes from initiation of the treatment session. The mean intensity levels for the live group were 16%, 19%, 21%, and 23% at the 0-, 5-, 10-, and 15-minute time points, respectively.

The sham treatment group was instructed that because the percutaneous electrode has microneedles that penetrate through the outer skin layers, they would not perceive the normal "pins and needles" usually associated with electrical stimulation. Throughout the entire sham treatment the machine was not turned on although the appropriate intensity buttons were pressed to simulate the live treatment.

Subjective Outcomes

Additionally, the Western Ontario and McMaster Osteoarthritis Index (WOMAC) questionnaire was completed by each patient prior to receiving the treatment and again at 48 hours post-treatment. The WOMAC questionnaire has proven valid in assessing pain, stiffness, and function of the osteoarthritic patient.[17] Posttest data identical to the pretest data was collected immediately post-treatment (0 hours) by the tester. At 6, 24, and 48 hours, post-treatment data were recorded by the patient and all study materials were mailed to the investigator at the completion of the study. A phone call to each patient at the 6-, 24-, and 48-hour time

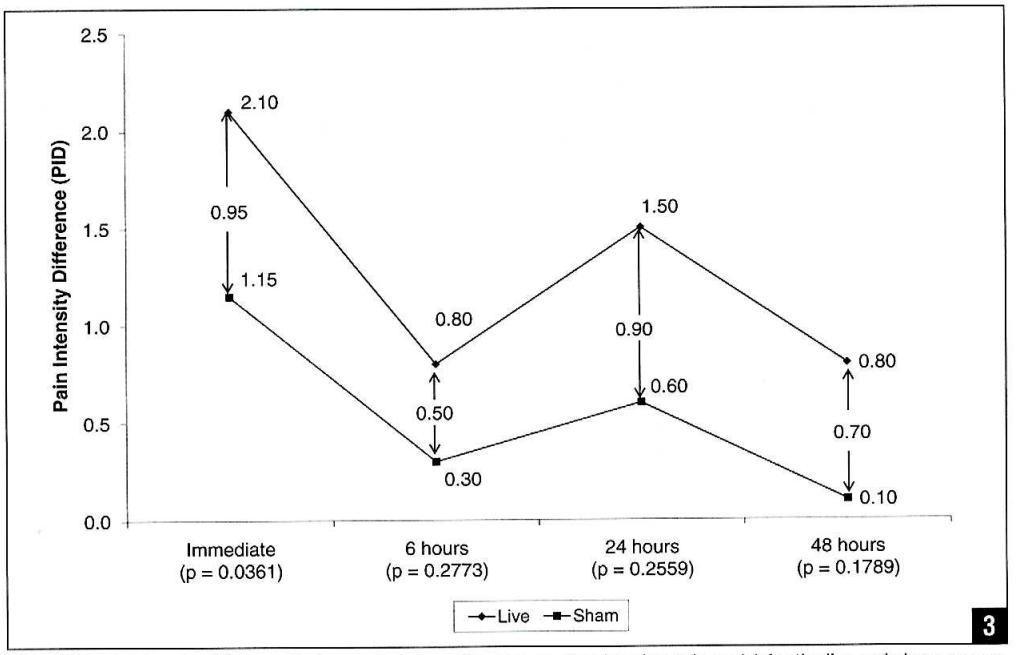

Figure 3: Pain intensity difference (values noted as centimeters on visual analog pain scale) for the live and sham groups.

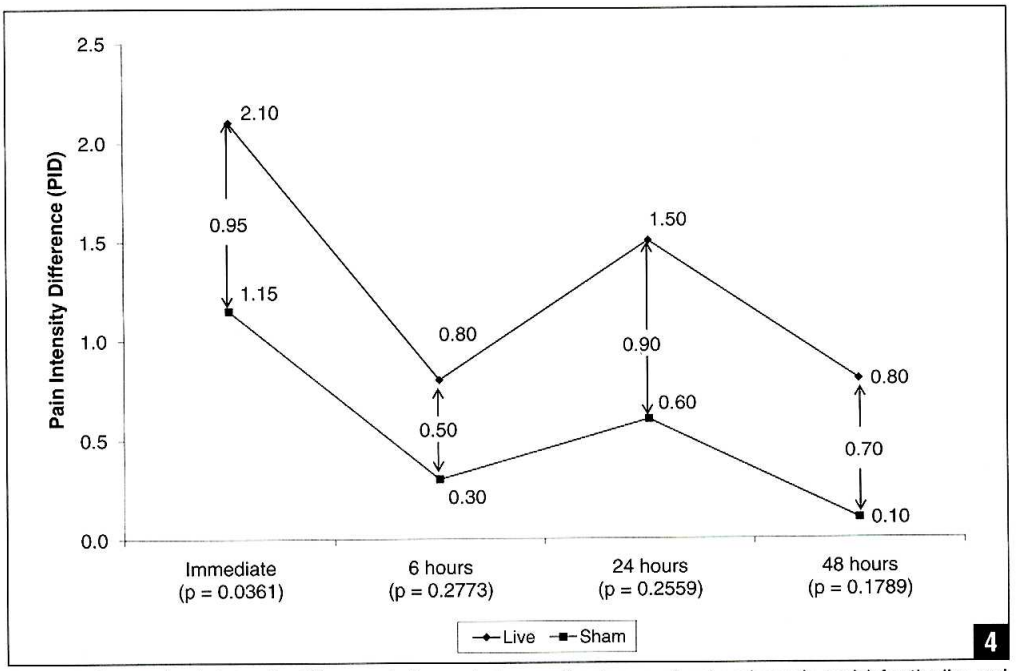

Figure 4: Summed pain intensity difference (values noted as centimeters on visual analog pain scale) for the live and sham groups.

points was performed to enhance patient compliance. The immediate, 6-, and 24-hour post-treatment data consisted of a visual analog pain scale and perceived overall improvement (0%-100%). The 48-hour data included the visual analog pain scale, perceived improvement, follow-up knee survey, and subjective questions regarding pain control and relief. Finally, a 1-week phone survey was conducted with subjective questions regarding adverse effects and medication use.

Statistical Analysis

Normally distributed continuous variables were analyzed with an analysis of variance (ANOVA) model with repeated measurements. Continuous variables that were normally not distributed were analyzed using the Wilcoxon test for pairwise comparisons. Categorical variables were analyzed with a chi-square test. Significance levels were set at $P<.05$.

RESULTS

Comfort and Safety

No serious adverse events were noted in either the live or sham groups. As seen in Table 2, there were no significant differences between live and sham groups with respect to comfort or adverse effects. One patient reported a mild erythematous maculopapular rash where the percutaneous electrode array was placed. This rash had resolved on its own within 24 hours. Three patients (1 live, 2 sham) reported mild tingling that resolved on its own within 6 hours of onset.

Pain Intensity Difference

Pain intensity difference was the primary measure of efficacy. Pain intensity difference is defined as the difference in visual analog pain scale noted at pretreatment (baseline) versus the visual analog pain scale noted at each post-treatment period. In this respect, figure 3 demonstrates that the live group had significantly greater efficacy than the sham group in the immediate post-treatment period ($P=.0361$). The live group's pain intensity difference was greater than the sham group's pain intensity difference by 9.5 mm, 5.0 mm, 9.0 mm, and 7.0 mm for

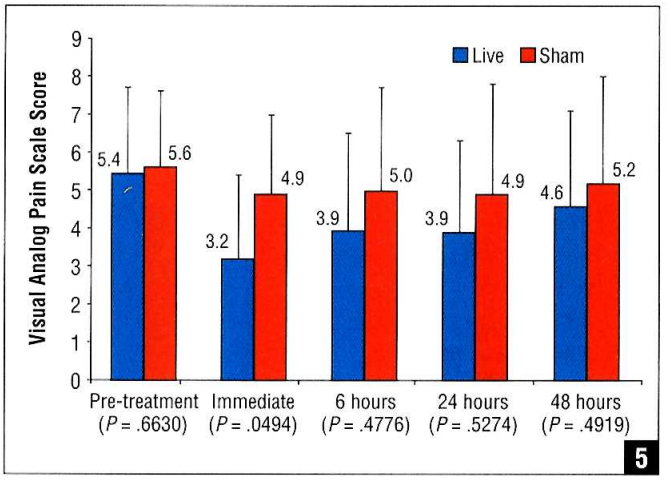

Figure 5: Raw visual analog pain scale scores recorded for live and sham groups. Significance is noted at the immediate post-treatment period.

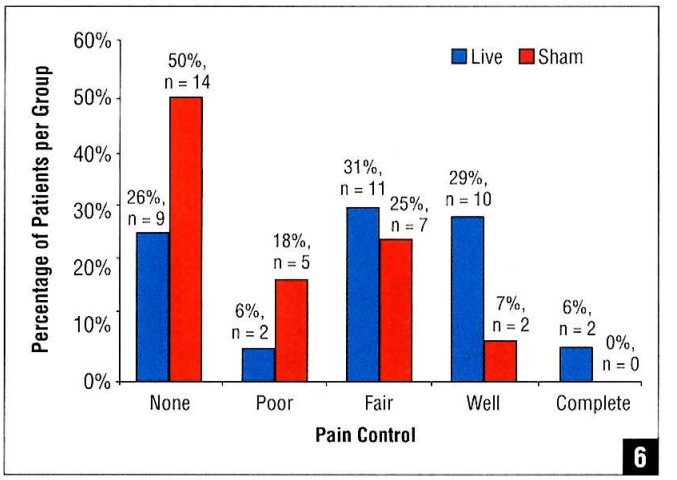

Figure 6: Distribution of pain control assessed at 48 hours post-treatment. The live group has significantly better pain control than the sham group (P=.039).

the immediate, 6-, 24-, and 48-hour post-treatment periods, respectively. Additionally, a trend was noted in improvement of the pain intensity difference in the live group as compared to the sham group >48 hours post-treatment.

An overall assessment of pain intensity difference was made by determining the median pain intensity difference over all post-treatment periods. The median pain intensity difference for the live and sham groups was 14.5 mm and 6.5 mm, respectively. This 8-mm variation in median pain intensity difference was significant (P=.0071).

Figure 4 demonstrates the live group's significantly greater efficacy compared to the sham group when evaluating the median of summed pain intensity difference scores for the immediate post-treatment period (P=.0361). In this case as well, a trend was noted in improvement in the live group as compared to the sham group over 48 hours post-treatment. Differences in summed pain intensity difference were 9.5 mm, 14.5 mm, 23.5 mm, and 30.5 mm for the immediate, 6-, 24-, and 48-hour post-treatment periods, respectively.

Visual Analog Pain Scale

The raw scores for the "current pain" reported as a visual analog pain scale score are summarized in Figure 5. The live group had a significantly reduced visual analog pain scale score compared to the sham group at the immediate posttreatment period (live score=3.2; sham score=4.9; P=.0494). At later time points, a trend was noted toward greater reduction in visual analog pain scale scores in the live group as compared to the sham group.

Pain Control and Pain Relief

Pain control reported at 48 hours post-treatment was significantly better for the live group than the sham group (P=.039). Figure 6 demonstrates the distribution of the patients' assessment of pain control. The live group had 35% and the sham group had 7% of patients with pain control described as either "well" or "complete."

When asked to grade their pain relief on a 0%-100% scale at 48 hours post-treatment, the live group had 42% pain relief and the sham group had 11% pain relief. This difference of 31% between the two groups is significant (P=.0103).

Patient Satisfaction

When asked "How much better do you feel?" patients in the live group had significantly higher satisfaction scores than the sham group for all post-treatment periods (Table 3). The live group was higher than the sham group by 33% (P=.0128), 20% (P=.0459), 35% (P=.0287), and 50% (P=.0007) for the immediate, 6-, 24-, and 48-hour post-treatment periods, respectively.

At 1-week follow-up, patient satisfaction was significantly higher (P<.0001) for the live group than the sham group (Figure 7). The live group had 77% and the sham group had 11% of their patients report a satisfaction level of "good," "very good," or "excellent."

Medication Use

At 1-week follow-up, the live group reported significantly less

Table 3

Responses to the Question: "How Much Better Do You Feel?"

	(%)			
	Live	Sham	Difference	*P* value
Immediate	45	13	33	.0128
Hours				
6	30	10	20	.0459
24	50	15	35	.0287
48	50	0	50	.0007

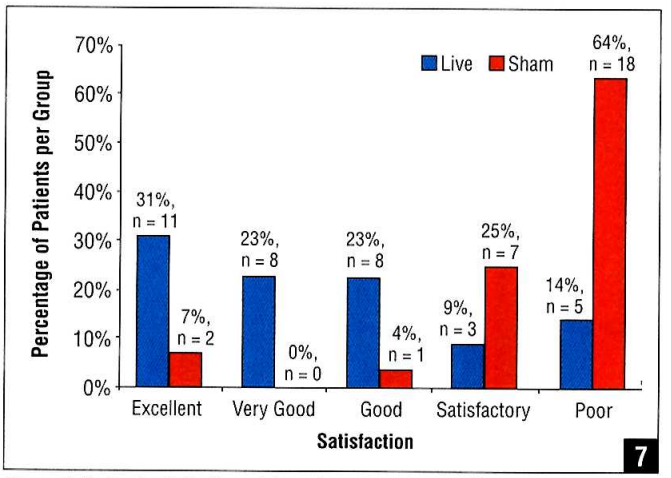

Figure 7: Patient satisfaction at 1-week post-treatment. Live group has significantly higher patient satisfaction than the sham group ($P<.0001$).

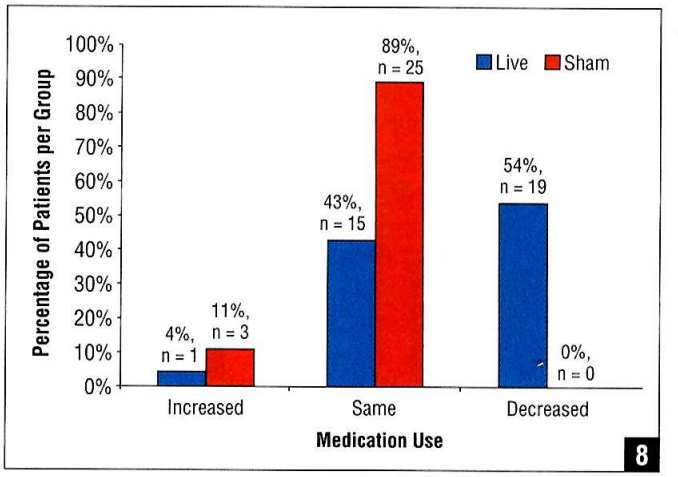

Figure 8: Medication use reported at the 1-week post-treatment. The live group had significantly less medication use ($P<.0001$) than the sham group.

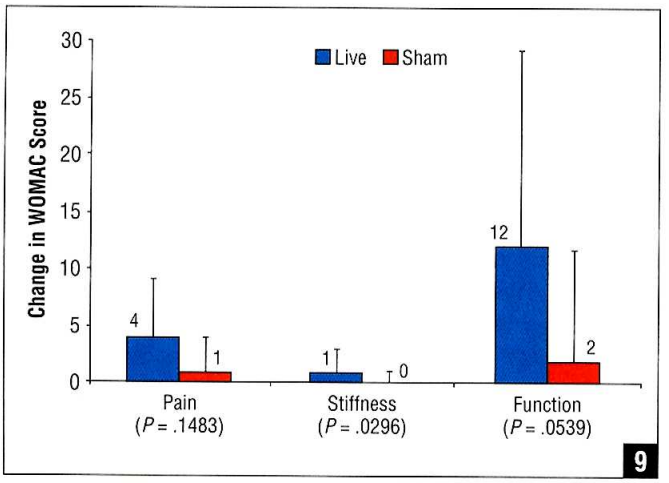

Figure 9: Change in WOMAC score from pretreatment to 48 hours post-treatment. The live group was statistically significantly different from the sham group for the stiffness assessment.

($P<.0001$) medication use than the sham group to treat their knee pain (Figure 8). The live group had 54% of its patients report a decrease in medication use, while the sham group reported no decreases.

WOMAC Scores

The change in WOMAC scores from pretreatment to 48-hour post-treatment for the live and sham groups are presented in Figure 9. The live group demonstrated greater improvements than the sham group for all WOMAC categories of pain (live=4, sham=1), stiffness (live=1, sham=0), and function (live=12, sham=2). The live group had a statistically significant improvement over the sham group with respect to the stiffness assessment ($P=.0296$).

Discussion

The Deepwave neuromodulation pain therapy device with percutaneous electrode arrays demonstrated safety and comfort in both the live and sham groups, with no serious adverse events reported in either group. Moreover, any minor events were tolerable and short-lasting. The live group had significantly greater efficacy over the sham group when evaluating pain intensity difference scores at the immediate post-treatment period. The live group pain intensity difference scores remained numerically superior to the sham group's scores at all later time points, but did not reach statistical significance. One consideration is that a larger sample number may lead to narrower distributions within each group, and thereby make the differences more likely to achieve statistical significance. Anther factor to consider is the improvement in function in the live group, as noted by the WOMAC scores, could reflect a greater level of activity in this group; and when combined with the reduction in analgesic consumption in the live group, these effects may have diminished the reduction in visual analog pain scores that the device would have achieved at later time points had those other variables remained constant.

Of particular note is that seven patients were lost to follow-up from the sham group and none were lost from the live group. Despite our emphasis on the importance of obtaining follow-up information, the patients lost to follow-up did not respond to our solicitations. It is likely that these patients were unhappy with the results of their treatment and did not feel compelled to contribute any further to the study. Thus, there is a possibility that if the results from these patients were obtained, the differences in pain intensity difference between the two groups would have been larger and achieved statistical significance.

Despite the lack of statistical significance with respect to the pain intensity difference at later time points, the differences between the live and sham groups became more

apparent when they were assessed subjectively. The live group had significantly better global assessment of pain relief and pain control than the sham group at 48 hours post-treatment. In the live group, 35% of the patients reported at least "well" or "complete" control of pain at the 48-hour time point, as compared to the 7% for the sham group. Additionally, 54% of the patients in the live group demonstrated a decrease in medication usage, which is overwhelming compared to 0% of the patients in the sham group. These reports are consistent with the significant level of satisfaction reported by the live group (77% of the patients reported good to excellent) as compared to the sham group (11% reported good to excellent).

Zubieta et al[18] reported that when a potential treatment has implied analgesic properties there are specific regional alterations in the brain leading to activation of the mu opiod receptors producing a placebo effect. Indeed, we observed a placebo effect in our sham group. The pain intensity difference for the sham group began at 11.5 mm immediately after treatment, and declined to 1.0 mm at 48 hours post-treatment. This range of pain intensity difference is consistent with the average pain intensity difference (6.5 mm on a 100-mm scale) in a recent systematic review of 27 clinical trials involving the treatment of pain.[19]

There were a few limitations to our study. The inherent natural history of osteoarthritic knee pain allows for daily variations of knee pain based on time of day and activity level. The patients' instructions were to continue their daily activities, however some patients were more active than others over the length of the study. Therefore, time of administration and changes in activity level may represent confounding variables in this pilot study. Also, because of its logistical feasibility, only a single treatment was administered for each patient. However, it is of general understanding that treatments analogous to the Deepwave percutaneous neuromodulation pain therapy device would be given on an "as needed" basis. The lack of this option in our study design may have contributed to the fading of the live treatment's efficacy over time. Finally, this study only had 24% power to conclude that the difference in pain intensity difference score at 48 hour posttreatment between the two groups was statistically significant (α=.05). Nonetheless, given the magnitude of the disparity in pain intensity difference scores between the live and sham treatment groups, our results merit further study for symptomatic treatment (with a Deepwave pain therapy device) of patients with knee osteoarthritis.

The Deepwave percutaneous neuromodulation pain therapy device has significant promise as an effective component of the nonoperative treatment algorithm for symptomatic osteoarthritis of the knee. The results of this pilot study have determined the safety and efficacy of a single dose treatment of the Deepwave percutaneous neuromodulation pain therapy device. Future studies should consider including administration of the treatment over a greater time period to mimic clinical application and assess a potential cumulative dose effect. The results from this pilot phase may be used to design a broader multicenter study that will be powered to provide greater data points leading to broader conclusions as to the treatment efficacy of the percutaneous Deepwave device.

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