BiowavePENS

Percutaneous Electrical Nerve Stimulation for the Treatment of Chronic, Acute or Postoperative Pain

Technical and Clinical Overview

biowavePENS

Biowave Corporation
biowave.com 1-877-BIOWAVE

What is **BiowavePENS?**

PENS = Percutaneous Electrical Nerve Stimulation

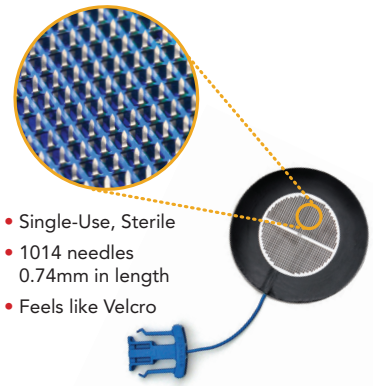
BiowavePENS delivers therapeutic electrical signals through a patented percutaneous electrode array to block pain signals at the surface of the nerve.

How **Does it Work?**

BiowavePENS is a frequency conduction pain block. The system is comprised of a neurostimulator that delivers high frequency electrical signals through a patented percutaneous electrode array which provides a direct conductive pathway through skin into deep tissue. The high frequency signals travel to the surface of nerves encompassing the pain site. Polarized structures including nociceptive pain fibers cause the high frequency signals to multiply together resulting in the formation of a therapeutic, low frequency active electrical field in a 3.5" diameter hemisphere beneath each percutaneous electrode.

The low frequency electrical field hyperpolarizes the C-fibers inhibiting action potential propagation, blocking the transmission of pain signals to the brain. In addition, the low frequency electrical field induces hypoesthesia in the region of the pain site. BiowavePENS is indicated to treat any type of chronic, acute or postoperative pain.

Percutaneous Electrode Array

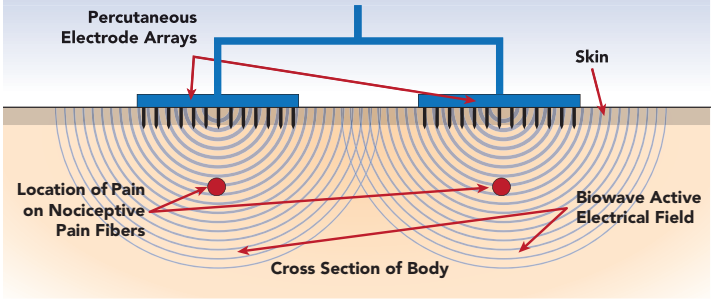


- Single-Use, Sterile
- 1014 needles 0.74mm in length
- Feels like Velcro

Biowave**PENS** is **superior** to TENS

BiowavePENS—Percutaneous Electrical Nerve Stimulation

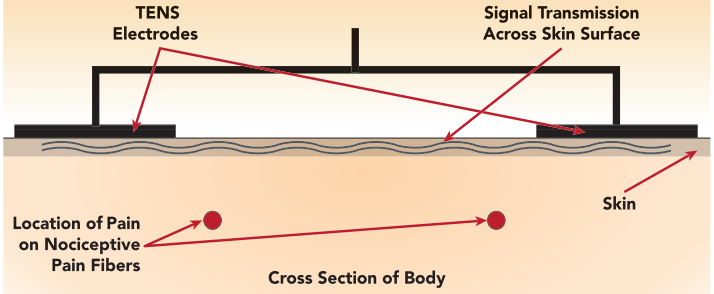
Transmits stimulation beneath the surface of skin directly to nociceptive fibers blocking the transmission of pain signals to the brain (Frequency Conduction Block Theory)



- Two high frequency signals pass through skin to the surface of nociceptive pain fibers. The polarization or charge at the surface of the nociceptive fibers causes a multiplication of the high frequency signals resulting in the formation of a low frequency electrical field.
- The low frequency electrical field encompasses the nociceptive pain fibers inside the body instead of trying to force low frequency through skin from the outside likeTENS, or needing to implant a lead next to the nerve like a spinal cord stimulator (SCS) or peripheral nerve stimulator (PNS)
- The result is instant, long lasting pain relief

TENS—Transcutaneous Electrical Nerve Stimulation

Transmits stimulation across the surface of skin which may act as a distraction to pain (Gate Control Theory)



- Low Frequency signals (1-180 hz) affect nerve fibers
- Problem - skin has high impedance & capacitance
- Low Frequency (LF) signals regardless of the shape of the waveform cannot pass through skin - LF signals only travel across the surface of skin
- The result is TENS never reaches the nociceptive pain fibers and only acts as a noxious surface sensation which MAY act as a distraction to pain

Features	BiowavePENS	TENS
Provides Long Lasting Pain Relief (Up to 72 Hours) Post Treatment[2]	✓	✗
Proven to Reduce Opioid Use[1,2]	✓	✗
Treatment Provides a Deep, Smooth, Comfortable Sensation[1,2]	✓	✗
Easy to Use - No Programming	✓	✗

Biowave **Clinical Benefits**

Clinically **Proven**

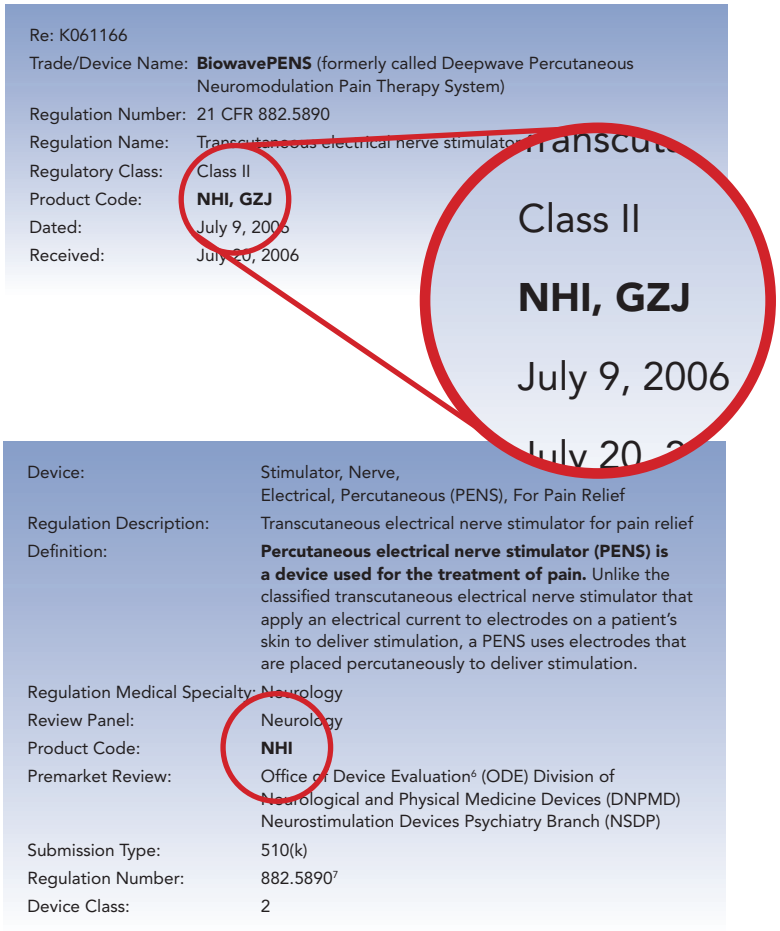
- **High Rate of Success.** Physicians report that more than 75% of patients respond to BiowavePENS treatments[1,2]
- **Substantial Reduction in Pain Scores.** Patients that respond, report a 50-75% reduction in their VAS pain scores after one thirty minute treatment[1,2]
- **Instant & Long Lasting Pain Relief.** Pain relief is instant as the patient increases the intensity and lasts up to 72 hours post treatment[1,2]
- **Reduced Opioid Use.** BiowavePENS treatments have been proven to provide up to a 50% reduction in patient controlled Opioid use[1,2]

75%

of patients respond positively to BiowavePENS neurostimulation

Biowave is the only medical device cleared by the FDA as PENS and indicated to treat any type of chronic, acute or postoperative pain.

FDA Product Code NHI = PENS
(Percutaneous Electrical Nerve Stimulation)



Re: K061166
Trade/Device Name: **BiowavePENS** (formerly called Deepwave Percutaneous Neuromodulation Pain Therapy System)
Regulation Number: 21 CFR 882.5890
Regulation Name: Transcutaneous electrical nerve stimulator
Regulatory Class: Class II
Product Code: **NHI, GZJ**
Dated: July 9, 2006
Received: July 20, 2006

Class II
NHI, GZJ
July 9, 2006

Device:	Stimulator, Nerve, Electrical, Percutaneous (PENS), For Pain Relief
Regulation Description:	Transcutaneous electrical nerve stimulator for pain relief
Definition:	**Percutaneous electrical nerve stimulator (PENS) is a device used for the treatment of pain.** Unlike the classified transcutaneous electrical nerve stimulator that apply an electrical current to electrodes on a patient's skin to deliver stimulation, a PENS uses electrodes that are placed percutaneously to deliver stimulation.
Regulation Medical Specialty:	Neurology
Review Panel:	Neurology
Product Code:	**NHI**
Premarket Review:	Office of Device Evaluation[6] (ODE) Division of Neurological and Physical Medicine Devices (DNPMD) Neurostimulation Devices Psychiatry Branch (NSDP)
Submission Type:	510(k)
Regulation Number:	882.5890[7]
Device Class:	2

Biowave **Clinical Studies**

1. Randomized controlled PENS study on the treatment of post-operative pain from TKA surgery - Hospital for Special Surgery, New York City. Podium Presentation at Eastern Orthopedic Association Annual Meeting, Oct 2008. Poster Presentation at AAOS Annual Meeting, February 2009

2. Randomized blinded controlled PENS study treating pain in grade 3 and 4 osteoarthritis of the knee - Rush University Medical Center, Chicago, IL. Published in ORTHOPEDICS June 2007

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Percutaneous Electrical Nerve Stimulation for the Treatment of Chronic, Acute or Postoperative Pain

Appendix – Clinical Studies

biowavePENS

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Musculoskeletal Clinical
Regulatory Advisers, LLC

MCRA Whitepaper

October 2017

Long Term Use of BiowaveHOME High Frequency Neurostimulation for the Treatment of Chronic Pain in Veterans Following Successful BiowavePRO Neurostimulation Therapy in Veterans Administration Hospitals.

Lindsay Kleinwaks, Associate, Regulatory Affairs
Margeaux Rogers, MS, Senior Associate, Regulatory Affairs
Dave McGurl, Director, Regulatory Affairs

White Paper
Long Term Use of BiowaveHOME High Frequency Neurostimulation for the Treatment of Chronic Pain in Veterans Following Successful BiowavePRO Neurostimulation Therapy in Veterans Administration Hospitals

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ABSTRACT

The opioid epidemic has created a $78.5 billion dollar issue in today's healthcare industry. The Veteran population is especially susceptible to opioid addiction as they are ten times more likely to develop an addiction and an estimated half of the Veteran population reports chronic pain radiating from at least one anatomical region [1]. Based on a 2014 VA hospital study, it was found that Veterans who were prescribed opioids for pain management spent an average of $13,605 in follow-up healthcare annually and those that were diagnosed as abusers of the drug were found to spend an average of $28,882 annually [13]. With opioids as one of the gold standard methods of pain management, it is not surprising that opioid addiction among Veterans has increased by 55% in recent years, creating a dire need for non-pharmacological, non-invasive, and non-addictive conservative treatment methods. BiowaveHOME, when paired with primary treatment at a VA-care facility with BiowavePRO, provides a new way to manage pain via electrical field generation in deep tissue inside the body. Sixty-six (66) Veterans were treated with BiowavePRO and then were given a BiowaveHOME to continue pain management on an as-needed basis. Ninety percent (90%) of the surveyed subjects reported a significant decrease in pain, increase in range of motion, or an increased ability to participate in activities of daily life after incorporating BiowaveHOME into their pain management regimen. Ninety percent (90%) of these same subjects reported that, compared to the Transcutaneous Electrical Nerve Stimulation (TENS) unit, a device based on electrical stimulation at the surface of skin, the BiowaveHOME was superior. Additionally, 58.7% of patients surveyed who were taking prescription pain medications either stopped using prescription opioids or reduced consumption. Patient satisfaction with the BiowaveHOME was measured by an overall decrease in pain, increase in quality of life, and a decrease in opioid consumption. In conclusion, the BiowaveHOME is a superior alternative to existing medical devices (i.e. a TENS unit) and is an attractive substitute for pain management by medications.

INTRODUCTION

In the United States an estimated 100 million people suffer from chronic pain conditions with opioid prescription pain medications used as the primary treatment [2]. The prevalence of chronic pain among U.S. Veterans is relatively high, with one study citing that half of a selected population of 300 Veterans reported at least one type of chronic pain. This same study reported that 75% of these patients were prescribed at least one analgesic for pain management, and that 44% of those patients prescribed analgesics were prescribed opioids [3]. Other studies report similar statistics, pointing to opioid prescription as a standard for the management of chronic pain. Excess or prolonged use of opioid treatment is a recognized gateway to the addiction crisis faced in the U.S.

In addition to the implications to the patient, the effects of opioid misuse can be felt socioeconomically, with opioid-related death tolls rising to nearly 100 Americans each day [4]. It was reported that approximately 50% of the prime-age male labor force is prescribed a daily regimen of pain medication, resulting in a negative impact on productivity and an increase in related-healthcare costs [5]. Due to the increasing reliance on pain medications, a large portion of the able-bodied workforce are unable to pass drug tests and resort to rehabilitation facilities to combat the addiction, further adding to the labor shortage. This epidemic affects men as well as women, of all races, across all socio-economic levels.

As of 2016, nearly two million Americans met criteria for prescription opioid abuse and

dependence, amassing aggregate costs of over $78.5 billion dollars. One-fourth of the economic burden was funded by the public sector, which includes Veterans' programs [6, 7]. Studies in Veterans Affairs (VA) hospitals of patients with chronic non-cancer pain highlight a link between prescription opioid dose and suicidal behavior [8]. In 2014, it was reported that the VA issued 1.7 million prescriptions for opioids to 443,000 Veterans for in-home pain management. As a result, the estimated number of Veterans with opioid addictions rose 55% between 2010 and 2015 [9, 10]. The high cost associated with opioid prescription, in addition to the fact that the Veteran population is ten times more likely than the average American to abuse opioids, has created a need for effective, non-opioid-based treatment options readily available to those impacted by chronic pain [1].

Although there is considerable documentation on the incidence and severity of both acute and chronic pain using traditional conservative methods in the general population, there is very little data regarding the utilization of non-invasive medical devices. Optimal analgesia encompasses the notion of providing optimal reductions in pain with increasing patient comfort, maximum patient satisfaction, and minimum related side effects for the prescribed treatment. Various treatment algorithms for the management of nonmalignant pain have been proposed which include a stepwise approach at managing pain with emphasis on utilizing the least invasive strategies whenever feasible. Still, pure opioid agonists continue to be the most commonly prescribed regimen for moderate to severe pain in many situations. A significant number of patients experience opioid related side effects, which limit their ability to achieve optimal analgesia and preclude them from various normal activities of daily living ("ADLs"). This is especially relevant to Veterans who are seeking non-opioid solutions to treating pain so that they can perform even simple daily activities to lead a normal life. Thus, there is an unmet need for alternative therapies that lessen the pain experienced by Veterans while minimizing side effects and the dependence of patient on prescription opioids.

PURPOSE

This study sought to examine the effectivity of the BiowaveHOME High Frequency Neurostimulator medical device as a new non-pharmacologic, non-narcotic, non-addictive, non-invasive way to manage pain and potential to reduce opioid use. This longitudinal (18-month long) study compiled data from 66 surveyed veterans in regard to their pain response to incorporating BiowaveHOME into their pain management routine.

MATERIALS/METHODS

The BiowaveHOME device was used to treat pain resulting from various chronic pain conditions in Veterans from three VA Medical Center ("VAMC") Hospitals: James A. Haley VAMC in Tampa, FL; Corporal Michael J. Crescenz VAMC in Philadelphia; and The Durham VAMC in Durham, NC.

Treatment Device

The BiowavePRO and BiowaveHOME neurostimulators are non-pharmacologic, non-narcotic, non-addictive, non-invasive adjunct of pain (Figure 1). The two devices work in an identical manner by delivery back and forth of a summation of two high frequency sinusoidal alternating current signals at 3,858 hz and 3,980 hz to a first electrode and then to a second electrode. The electrodes are placed directly over one or two locations of pain.

Figure 1: BiowaveHOME Neurostimulator

The mechanisms of action that result from the electrical field generated from Biowave devices are similar to chemical anesthetics and are based on Frequency Conduction Block Theory [14]. This is in contrast to Transcutaneous Electrical Nerve Stimulation (TENS) devices which are based on Gate Control Theory which provide a noxious sensation at the surface of skin which may act like a distraction to pain, but which do not block the pain signal.

The electrodes through which the high frequency signals are delivered consist either of:

1. B-set (Figure 2): two 2.0" diameter round electrodes for (i) treating two distinct locations of pain, (ii) the origin of pain and most proximal

location of pain to the origin (for example in the case of a radiculopathy) or (iii) one large area of pain (the electrodes are placed one inch apart from one another).

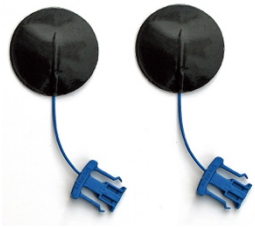

Figure 2: B-Set Electrodes

2. E-set (Figure 3): one 1.375" diameter round electrode placed directly over a single location of pain and one 2" x 4" rectangular dispersive electrode placed over a bony prominence which is a comfortable location to receive stimulation.

Figure 3: E-Set Electrodes

Study Enrollment

In order to participate in the study, subjects had to meet the inclusion/exclusion criteria, outlined below.

Inclusion Criteria

1. Subjects may be male, female or transgender of any race
2. American Society of Anesthesia Physical Classification: ASA 1-3 [11]
3. Ages 16 - 80 yr
4. Subjects must have been using BiowaveHOME for a period of at least 6 months.
5. Subjects must respond to at least one or more treatments from a BiowavePRO neurostimulator at their VAMC. Response includes at least one of the following:
    a. Reduction in VAS pain score of ≥30%,
    b. Increase in range of motion (ROM) of ≥ 10%;
    c. Reduction in pain medication consumption;
    d. Improvement in ADLs.
6. Subjects must be able to understand and operate a BiowaveHOME neurostimulator
7. Subjects must be able to provide a verbal response to a patient questionnaire

Any Veteran who was injured and had a chronic pain condition was eligible to participate. Treatment with Biowave HOME could be performed on an as needed basis or until the condition resolved.

Exclusion Criteria

1. Allergy or intolerance to adhesive materials
2. Clinical evidence of cardiovascular (history of cardiac arrhythmias), pulmonary, renal, psychological, hepatic, neurological (seizures), hematologic, or endocrine abnormalities
3. Rash or wounds in the area where electrodes need to be placed
4. History of pacemaker or implantable AICD

From the initial pool of Veterans eligible for the study, 187 were contacted for responses to the study. Of the 187 potential subjects, sixty-six (66) responded to the 9-question survey.

Treatment Algorithm

Subjects were first treated using a BiowavePRO neurostimulator in a VA Medical Center either in a Pain Clinic, Physical Medicine and Rehabilitation (PM&R) Clinic or in a Spinal Cord Injury (SCI) Clinic.

Subjects were treated three times over a one to three week period. Treatment duration was 30 minutes. Subjects were evaluated following each treatment. At the end of the three treatments, subjects were issued a BiowaveHOME unit through the Department of Prosthetics, if:

1. The subject had ongoing pain management needs; AND
2. The subject's response to the BiowavePRO treatment in the clinic included one of the following:
    a. Reduction in their VAS pain score of ≥30%,
    b. Increase in range of motion (ROM) of ≥ 10%;
    c. Reduction in pain medication consumption;
    d. Improvement in ADLs.

Table 1: Demographics Information

N=66	Male n (%)		Female n (%)	
Study Gender Distribution	61 (92.5)		5(7.5)	
N=66	**Acute n (%)**	**Chronic n (%)**	**Both n (%)**	**Non-Response n (%)**
Type of Pain	5 (8)	51 (77)	8 (12)	2 (3)

Subjects then continued treatment with Biowave-HOME at their home on an as needed basis. BiowaveHOME outputs the identical waveform at the same frequency and intensity as BiowavePRO. Electrode placement was identical at home as compared to treatment in the clinic. Treatment duration at home is also 30 minutes.

Exactly as in the clinic, subjects were instructed to increase the intensity of their BiowaveHOME unit to a strong but comfortable sensation. As the body adapts to the internal electrical field, the sensation from the internal electrical field diminishes, and subjects were instructed to keep increasing the intensity level to maintain a steady state strong sensation throughout the duration of the 30-minute treatment. Subjects were then instructed to continue to treat on an as needed basis.

Subjects who had been issued Biowave devices over a period of 18 months had been contacted and asked a series of 9 questions relative to their experience using the Biowave device:

1. *Do you have acute pain or chronic pain?*
2. *What part of your body are you treating?*
3. *Have you reduced your pain meds or reduced your opioids?*
4. *What other treatments have not worked for you?*
5. *How does Biowave compare to TENS?*
6. *What do you like about Biowave?*
7. *How often do you use Biowave?*
8. *If you're not using it any more, how come? (For example: pain is gone) Are you undergoing any other form of treatment?*
9. *Has Biowave helped improve your quality of life? How*?

Information was captured using a Salesforce database.

RESULTS

Effectiveness

For this study, the responses of 66 veterans meeting all inclusion criteria were analyzed for a reduction in pain, increase in range of motion, reduction in pain medication consumption, and improvement in activities of daily living by way of a 9-question survey.

The results compiled within this section are responses provided by surveyed Veterans after up to 18 months of in-home treatment with Biowave-HOME. The majority of subjects (92.5%) in the study were male (Table 1). Seventy-seven percent (77%) of surveyed subjects reported having chronic pain, 8% reported having acute pain, and 12% reported having both chronic and acute pain before the study (Table 1).

Categorizing the location of pain, 36% of the subjects reported back pain alone while the majority (52%) reported pain presenting in multiple locations (Table 2). The majority of subjects (89%) failed a previous conservative treatment such as TENS, opioid, or physical therapy ("PT") (Table 3).

Table 2: Pain Location

N=66	n (%)
Upper Extremities Only[A]	5 (8)
Lower Extremities Only[B]	1 (2)
Neck	2 (3)
Back	24 (36)
Multiple Regions[C]	34 (52)

[A] Upper extremities include shoulder, arms, and/or hands
[B] Lower extremities include hips, legs, knees, and/or ankles.
[C] Multiple Regions include back, neck, upper extremities, and/or lower extremities

Table 3. Previous Failed Treatments

N=66	n (%)
TENS Treatment Alone	19 (29)
TENS Treatment in Combination with Other Therapies[A]	32 (48)
Other Treatments	8 (12)
No Answer Provided	7 (11)
Total failed using TENS alone or in combination	51 (77)

[A]Other therapies include dry needling, injections, opioids, physical therapy, chiropractic care, acupuncture, nerve block, or IFC.

When surveyed about frequency of utilization, 95.1% of subjects reported regular use at up to 18 months. A high rate of subjects (85.6%) were utilizing the device multiple times a week or more. Of those subjects 50.8% were using it daily (Table 4).

Table 4. Subject Frequency of Use for Biowave

N=66	n (%)
Multiple times a day	20 (30.3)
Once daily	12 (18)
Multiple times per week	22 (33.3)
Once a week	6 (9.1)
As needed	3 (4.5)
Stopped Using	3 (4.5)
Total Using Regularly	90.9%

Out of the subjects who were previously treated with TENS units, 90.7% of surveyed subjects reported that the BiowaveHOME was superior to the TENS unit (Table 5) and over 84.8% of all surveyed subjects say that their pain level had decreased, their range of motion has increased, or their activities of daily life have improved since incorporating the BiowaveHOME into their pain management regimen. Out of the subjects taking pain medication at the beginning of the study, 58.7% have either stopped taking or have significantly reduced the consumption of prescription pain medications since beginning treatments with the BiowaveHOME pain management device (Table 6).

Table 5. Comparison of Biowave to TENS

N=54	n (%)
BiowaveHOME superior to TENS treatment	49 (90.7)

Table 6. Effect on Pain Medicine Consumption

N = 55	n (%)
Consumption was reduced	26 (47.3)
Consumption was eliminated	6 (10.9)
Consumption remained unchanged	23 (41.8)

Eighty-four percent (84.8%) of all subjects surveyed at the end of the study said that their quality of life was improved by introducing BiowaveHOME into their pain management routine (Table 7).

Table 7. Overall Effect on Life

N = 66	n (%)
BiowaveHOME improved quality of life	56 (84.8%)
BiowaveHOME did not improve quality of life	5 (7.6%)
Not sure	5 (7.6%)

Safety

There were no reports of any burns, or any electro-thermal injury or any other adverse events.

DISCUSSION

This study sought to assess the effectiveness of a non-pharmacological alternative for pain management, the BiowaveHOME device. This is the first study to evaluate long term use (6 to 18 months) of the BiowaveHOME device to treat chronic pain in Veterans. This study demonstrates that Biowave is an effective non-pharmacological, non-invasive, non-addictive pain treatment solution. Successful treatment in the physician's office, clinic or hospital with the BiowavePRO high frequency neuro-stimulator (77-85% of those treated receive a 50%-100% reduction in VAS pain scores and an improvement in function for up to 24 hours post treatment [15]) can be continued cost effectively at home on an as needed basis with an outpatient treatment regimen using the BiowaveHOME high frequency neurostimulation medical device.

As of 2016, nearly two million Americans met criteria for prescription opioid abuse and dependence, amassing aggregate costs of over $78.5 billion dollars. One-fourth of the economic burden was funded by the public sector, which includes Veterans' programs [6, 7]. The study was quick to note that these costs do not account for the economic value of loss of productivity and quality of life. The high cost associated with opioid prescription, in

addition to the fact that the Veteran population is ten times more likely than the average American to abuse opioids, has created a need for effective, non-opioid-based treatment options readily available to those impacted by chronic pain. The study demonstrates that Biowave can be a viable alternative or adjunct to chronic pain management and potentially reduce the patients' opioid use.

Another form of conservative therapy that has provided a non-pharmacologic, non-narcotic, non-addictive, non-invasive way to manage pain is the Transcutaneous electrical nerve stimulation, or TENs unit, which is based on the "gate control theory" of pain which focuses on masking pain signals, providing relief for a short period of time. Mixed reviews about if TENs delivers pain relief to common areas of chronic pain has created yet another unmet market need for an effective alternative [12]. The technology behind Biowave is based on the "frequency conduction block theory," which blocks pain signals by preventing the sodium – potassium ion exchange across the membrane of nociceptive pain fibers thereby preventing action potential along the pain fibers. This study found that subjects preferred the Biowave device over TENS device for treatment. While the rationale for preference was not part of this study, it is likely due to the effectiveness of pain reduction as well as treatment comfort that subjects experience with Biowave devices as compared to a TENS treatment.

BiowaveHOME, in addition to providing a non-pharmacological, effective pain management alternative, provides a financially attractive alternative option. While this study did not directly compare the potential cost savings to the VA system, the implications of this are not to be understated. As previously stated, the Veteran population is ten times more likely to develop an opioid addiction than the average American and the pool of Veterans currently battling opioid addiction from using opioids as a side effect of pain management is close to 443,000. The distribution of the BiowaveHOME to chronic pain sufferers could potentially drastically decrease the yearly healthcare budget allocated to dealing with the opioid epidemic and while increasing the quality of life of those affected by addictive methods of pain management. Based on a 2014 VA hospital study, it was found that Veterans prescribed opioids for pain management spent an average of $13,605 in follow-up healthcare annually and those that were diagnosed as abusers of the drug were found to spend an average of $28,882. Outpatient service costs for Veterans prescribed opioids and diagnosed with addiction spent close to $11,192 annually [13]. Comparatively, BiowaveHOME is a low cost alternative, with nearly one-tenth the cost of yearly outpatient services in the first year and nearly one twentieth annual cost for subsequent years.

Based on the results of the study, BiowaveHOME is an effective, well-received non-pharmacologic alternative to the existing pain management options and greatly improves patient quality of life.

CONCLUSIONS

Overall, the BiowaveHOME was found to be well tolerated by the majority of study subjects. The subjects expressed great satisfaction with the treatments, suggesting that this method of pain management is an alternative to existing medical devices (i.e. TENS units) and is an attractive substitute for pain management by medications.

Biowave can help healthcare providers provide their patients with a continuum of care. The first step is to verify treatment success with a BiowavePRO high frequency neurostimulator in a clinic or hospital setting. If the patient responds successfully to treatment in the clinic and has ongoing pain management needs, the provider can then issue a BiowaveHOME high frequency neurostimulator to the patient so the patient can continue to manage their pain at home on an as needed basis and with a reduced level of opioids.

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A Randomized Placebo-Controlled Study To Determine Safety and Efficacy In Terms Of Pain Reduction, Increased Range Of Motion, And Reduced Pain Medications, For A Novel Percutaneous Neuromodulation Pain Therapy Device ("BiowavePENS") Following Post-Operative Treatments For Total Knee Replacement Procedures.

Location:	**Hospital for Special Surgery New York, NY**
Investigators:	**Tony Wanich MD, Jonathan Gelber MD, Scott Rodeo MD, Russell Windsor, MD**

Podium Presentation:	**Eastern Orthopaedic Association 39th Annual Meeting, October 22-25, 2008, Ritz-Carlton, Lake Las Vegas, Henderson, Nevada**
Poster Presentation:	**American Academy of Orthopaedic Surgeons 2009 Annual Meeting, February 25-28, 2009, Las Vegas, Nevada**

Introduction

It is estimated that 300,000 total knee replacements (TKR) are performed annually in the United States for the treatment of end stage arthritis.[1] Improvements in technique and implant design have resulted in a patient satisfaction rate greater than 85% in TKR patients. Despite the long term success of TKR, post-operative pain control following TKR remains a difficult problem.

Several pharmacologic and nonpharmacologic approaches exist to alleviate post-operative pain and improve functional status. Nonpharmacologic therapies include cryotherapy and transcutaneous electrical nerve stimulation (TENS)[2,3,4,5]. Pharmacologic treatments include an epidural block, peripheral nerve block, intra-articular morphine, systemic opioids, corticosteroids, nonsteroidal anti-inflammatory agents (NSAIDs) including Cox-2 inhibitors and antidepressants. Opioids remain a controversial choice primarily because of concerns of addiction and side effects. In addition, opioids are not particularly effective in alleviating neuropathic pain and pain with movement. While regional pain control has demonstrated improved analgesia with a safer side-effect profile, it remains an invasive procedure which poses its own set of risks.[6]

The concept of using electricity for the reduction of acute pain is not new. The earliest written records of this come from the classical Greek civilization which used electrical fish to numb painful areas of the body.[7] In 1859, Garratt used electrical anesthesia during tooth extraction, and recommended its use for relief of toothache, jaw ache, and trigeminal neuralgia. Because of the varied success and irreproducible results, electrical anesthesia was used sparingly throughout the first half of the 20th century. It was not until 1965 when Wall and Melzack developed the gate control theory of pain transmission that electronic dental anesthesia began to receive serious scientific study. [8]

The gate theory states that the brain can only register and respond to a limited amount of neural input from any given point of origin at any given moment. If a more powerful or more conducive sensory impulse is introduced into the neural cycle, it can override the slower pain impulse, causing the brain to perceive the sensory impulse and not the original pain impulse. A significant drawback to this type of electrical pain control is the unwanted motor side effects on muscles, and the inability of the TENS signal to penetrate into deep tissue.

Another theory for inhibiting the transmission of pain signals is known as frequency conduction block or hyperpolarization.[9] Hyperpolarization occurs when action potential propagation is prevented

thereby interrupting transmission of pain impulses. Hyperpolarization is thought to be the mechanism of action for local chemical anesthesia.

Percutaneous neuromodulation (also known as Percutaneous Electrical Nerve Stimulation or PENS) is a new technology based on the theory of hyperpolarization for inhibiting pain transmission. A new system called BiowavePENS (which is comprised of a BiowavePRO neurostimulator (Figure 1) and two Biowave Percutaneous Electrode Arrays (Figure 2)) utilizing this technology has been developed, and has deeper tissue penetration than TENS with preliminary studies demonstrating superior results[10,11]. The device sends a premixed modulated envelope of two high frequency electronic wave forms ("feed signals") between two Biowave percutaneous electrode arrays ("PEAs") (Figure 2). PEAs are a microneedle based technology comprised of 1014 needles that are 0.74 millimeters in length within a 2.5 inch diameter sterile patch. The PEAs facilitate the delivery of the feed signals through the skin into deep tissue. Polarized structures in the deep tissue force a further multiplication of the feed signals (a Fourier Transform) resulting in a new spectrum of signals. One of the resulting components formed in the new spectrum is a low frequency signal in the form of an electric field. It is believed that this low frequency electric field inhibits the sodium – potassium ion exchange across the membrane of the C-fiber thereby preventing action potential propagation. The volume of tissue affected is dependent upon 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 in approximately a 2.5 inch volume of tissue beneath each percutaneous electrode.

BiowavePRO®
Neuromodulation
Pain Therapy System

Figure 1

Biowave
Percutaneous Electrode Array (PEA)
• 1014 microneedles
• 2.5 inch diameter patch

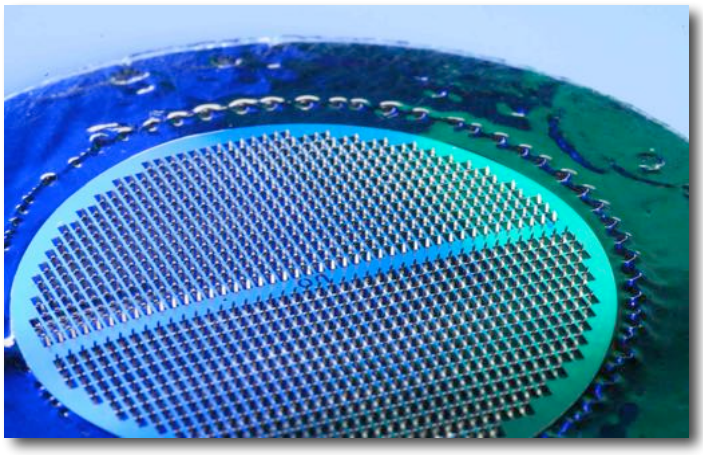

Figure 2

We hypothesize that the use of BiowavePENS (BiowavePRO neurostimulator with Biowave Percutaneous Electrode Arrays) as a complimentary therapy is efficacious and safe in reducing the severity of acute and chronic pain in patients following TKR surgery, while reducing patient need for opioids. We evaluated this hypothesis in a randomized, placebo-controlled, patient-blinded study.

Materials and Methods

This prospective, randomized clinical trial was initiated after receiving approval from an independent institutional review board. From July 2005 to July 2006, patients undergoing primary total knee

replacement were recruited to take part in this study. All patients were operated on by two fellowship trained orthopaedic surgeons.

Patients were included if they were male or female between 50 and 75 years of age undergoing primary, unilateral total knee replacement. The underlying diagnosis was osteoarthritis in all cases, and all patients had a baseline score of ≥30 mm out of 100 mm on the Visual Analog Scale (VAS). Patients were excluded if they had a history of epilepsy, implantable devices (eg pacemaker, AICD, pump, etc.), substance abuse within 6 months of surgery, or involvement in another clinical trial within 30 days of screening.

Twenty-three (23) patients were ultimately recruited for participation in this study and randomized to either an experimental or control group. Patients were blinded to the results of their randomization. All patients randomized to the control group completed the study, while 2 patients from the experimental group withdrew prior to completion of the study. These two patients withdrew because they were unwilling to comply with twice daily treatments secondary to fatigue.

All patients underwent primary total knee replacement by one of two fellowship trained orthopaedic surgeons. Surgery was performed under epidural anesthesia utilizing a standard medial parapatellar approach under tourniquet. All knees implanted were cemented, posterior stabilized knees. Following completion of surgery, sterile percutaneous electrode arrays (PEAs) were placed on the medial and lateral aspects of the operated knee at the level of the joint line. The knee was then covered with a sterile dressing, making sure the ends of the electrode were accessible outside of the dressing.

Patients were given a dilaudid/bupivicatine epidural PCA for pain control postoperatively. Continuous passive motion (CPM) was initiated on all patients immediately postoperatively in the recovery room.

Experimental Group

BiowavePENS treatments were initiated in the experimental group following removal of the epidural at 36-48 hours post surgery. Patients received twice daily treatments 30 minutes prior to morning and evening continuous passive motion (CPM) sessions. Sessions were spaced 8 to 12 hours apart and lasted 30 minutes. Patients continued to receive treatments until discharged from the hospital.

All treatments were performed by the study investigators. The initial intensity of the treatments was determined by gradually increasing the intensity until a strong but comfortable tingling/pressure sensation was felt inside the knee. At this point there is a quick adaptation to the electric field and the edge of the sensation felt by the patient will begin to diminish within several seconds. Once this point was indicated by the patient, the intensity was increased until the sensation was achieved. This process was continued until the sensation in the knee remained strong with no evidence of diminution. This was considered the therapeutic level at which the remainder of the treatment was continued.

Each time the intensity was increased, the time of the increase and the new level of intensity (0% - 100% of max intensity) was recorded for the entire treatment. The therapeutic level of each session was then used to optimize all subsequent treatments.

Control Group

Treatments in the control group were also initiated following removal of the epidural at 36-48 hours postoperatively. All treatments were administered by the study investigators. After connecting patients to the study device, sham treatments were administered with the device set to 0% intensity. 30-minute treatment sessions were administered 30 minutes prior to morning and evening CPM sessions scheduled 8-12 hours apart. Treatments were continued until discharge.

Outcome Measures

Prior to each treatment session, vital signs (blood pressure, heart rate, temperature and respiratory rate) were recorded for all patients. Before and after each treatment, patients completed a Brief Pain Inventory (BPI) questionnaire. The questionnaire included subjective ratings for pain classified as either none, minimal, moderate, or severe. These categorical variables were then converted to ordinal variables for data analysis (None = 0, Minimal = 1, Moderate = 2, Severe = 4). The BPI questionnaire also included a Visual Analog Scale (VAS) pain score. The type and dose of all medications taken by patients was also recorded.

Results

Twenty one patients ultimately completed the study, with 11 in the experimental group and 10 in the control group. There was no statistical difference in the average age between the control group (avg 69.8 yr) and the experimental group (72.3 yr). Women comprised 70% of the subjects in both groups. There was a significant reduction in patient's subjective rating of pain before and after treatments in the experimental group ($p < .05$) while there was no change in the control group. The VAS pain score (Figure 3) was significantly reduced for patients in the experimental group from before to after treatments ($p < .05$) as compared to the control group.

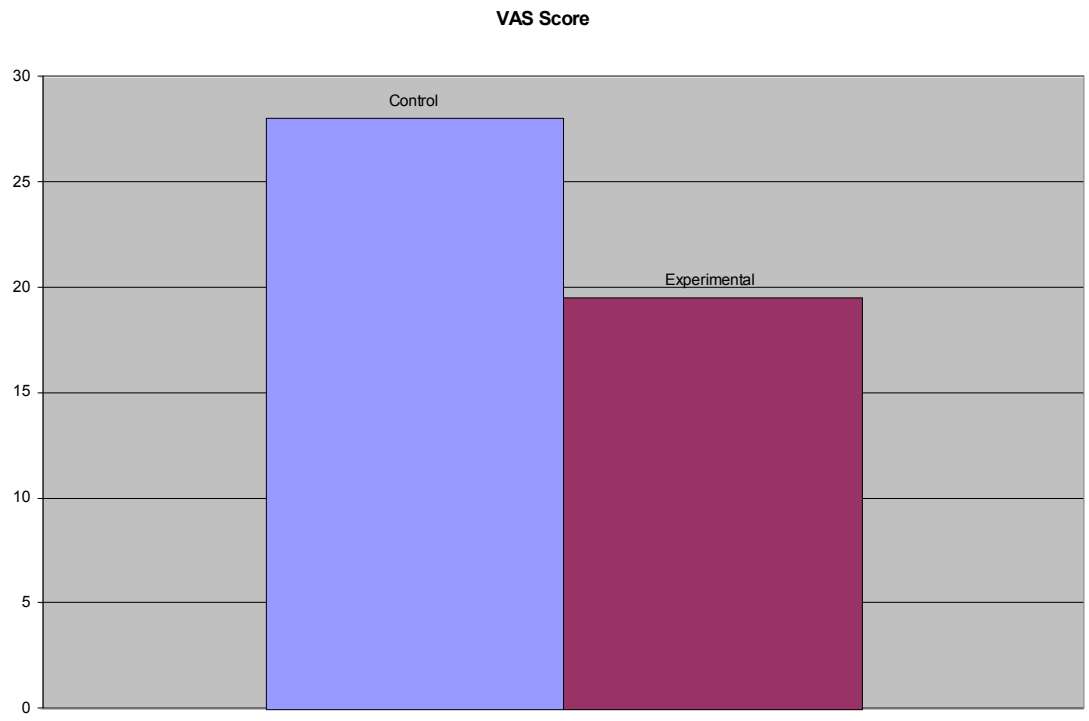

Figure 3: VAS Score

There was a trend towards decreased opioid use (Figure 4) in the experimental group as compared to the control group, however, this difference was not statistically significant ($p = .09$).

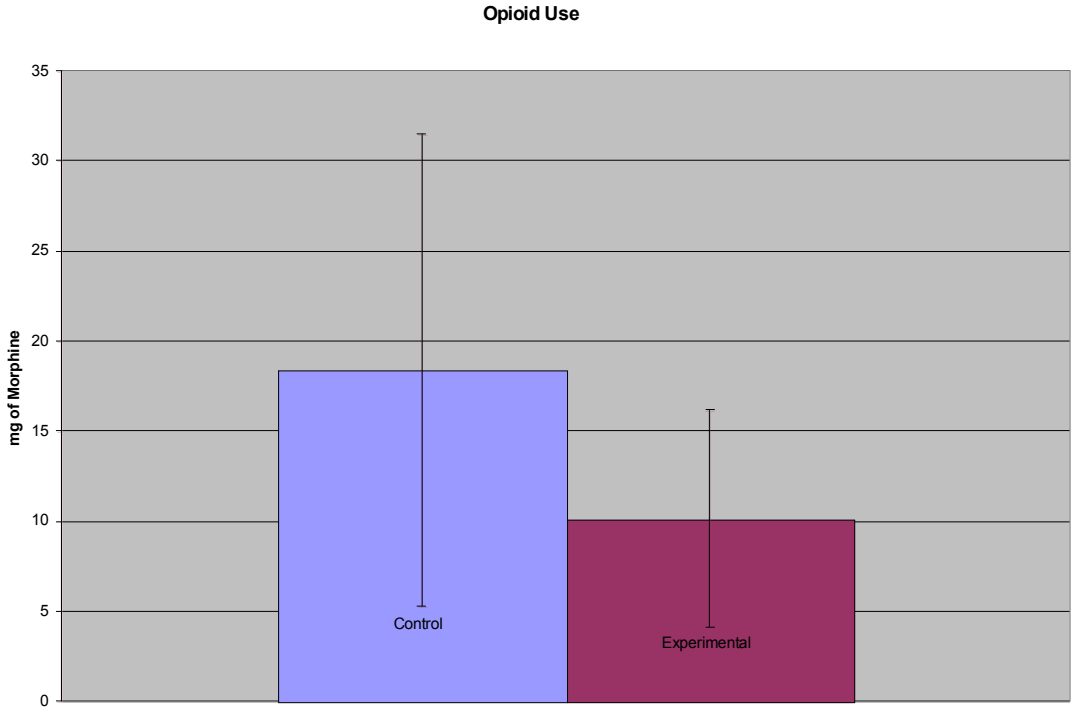

Figure 4: Opioid Use

There were no infections which developed in the perioperative period. There was no evidence of skin irritation or breakdown in any patients. One patient in the experimental group complained of tenderness over the medial PEA which was replaced with a new PEA with improvement in the discomfort.

Conclusion

Postoperative pain following Total Knee Replacement remains a difficult problem leading to delays in rehabilitation and prolonged hospitalization.[12,13] A number of multimodal pain regimens have been utilized to minimize the use of opioids given their significant side effects.[14,15,16] While transcutaneous electrical nerve stimulation (TENS) appears to be effective in the treatment of knee osteoarthritis, it has not been shown to be efficacious in the treatment of pain following TKR.[17,18] The BiowavePENS system (BiowavePRO neurostimulator with Biowave Percutaneous Electrode Arrays) incorporates a significant modification of TENS technology with the use of microneedles incorporated into a percutaneous electrode array which facilitates delivery of the electrical signals into deeper tissue while also creating a unique electric field with increased intensity. Based on results from this study, the BiowavePENS system appears to be effective in reducing the subjective measures of pain with a trend towards decreased opioid use in patients following total knee replacement.

There are several limitations to this study. The number of patients enrolled was relatively small and follow up was only monitored during the hospitalization. While there was a trend towards lower opioid use in the experimental group, the study was underpowered to examine this question. Post-hoc power analysis reveals a total of 51 patients would have been required to avoid a Type-II error with the given results. This study was designed to examine the short-term perioperative impact of the BiowavePENS system. Longer term impact of the device is planned in future studies. The VAS was primarily designed to monitor chronic pain, but has been shown to correlate with acute, postoperative measures.[19]

At the initiation of the study, there was some concern that the use of the percutaneous electrode arrays with microneedles may increase the risk for infection. In our study, we did not see any evidence of superficial or deep infection related to the device. Despite the aforementioned limitations, the BiowavePENS system appears be a promising modality in the treatment of postoperative pain following total knee arthroplasty. These early results have led us to pursue a follow up study incorporating a larger number of patients. In addition to measures of pain and opioid use, the follow up study will also evaluate the effect of the device on length of stay due to decreased narcotic side effects and impact on achieving post-operative range of motion.

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

Richard W. Kang, MD, MS; Paul B. Lewis, MD, MS; Adam Kramer, ATC; Jennifer K. Hayden, RN, MSN; Brian J. Cole, MD, MBA

This pilot study presents the initial results for a percutaneous neuromodulation pain therapy device (BiowavePRO with Deepwave Percutaneous Electrode Arrays) 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 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.

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

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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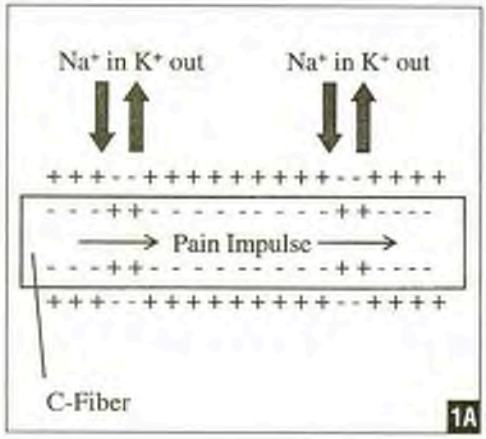

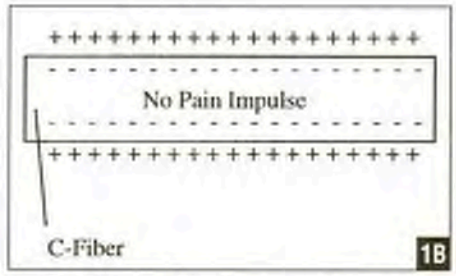

Figure 1: Deepwave (Biowave Corporation, Norwalk, Conn) mechanism of action via frequency conduction block. Normal propagation of pain signal along pain fibers (C-fibers) (A). Deepwave electric field interrupts sodium/potassium ion exchange, thereby inhibiting the cell wall from changing polarity and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

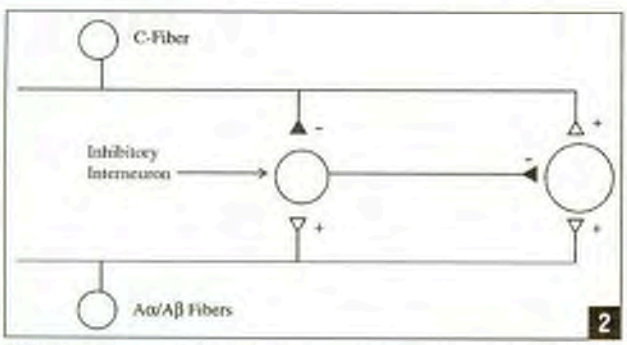

Figure 2: Deepwave (Biowave Corporation, Norwalk, Conn) mechanism of action via the gate control theory. The Deepwave may also activate the Aα/Aβ fiber, which occurs at both the inhibitory interneuron and projection fiber, thus causing a suppression of the pain sensation.

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.

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

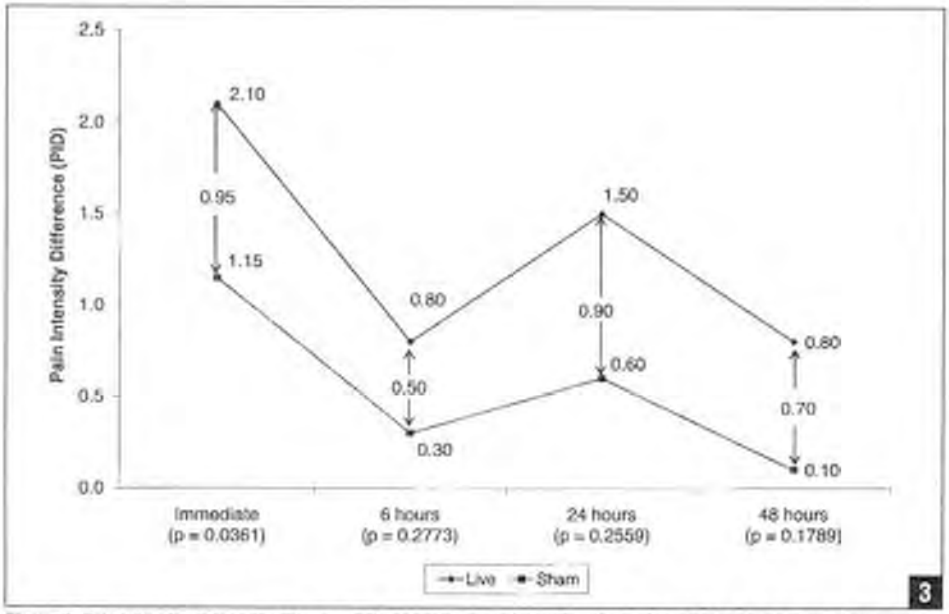

Figure 3: Pain intensity difference (values noted as centimeters on visual analog pain scale) for the live and sham groups.

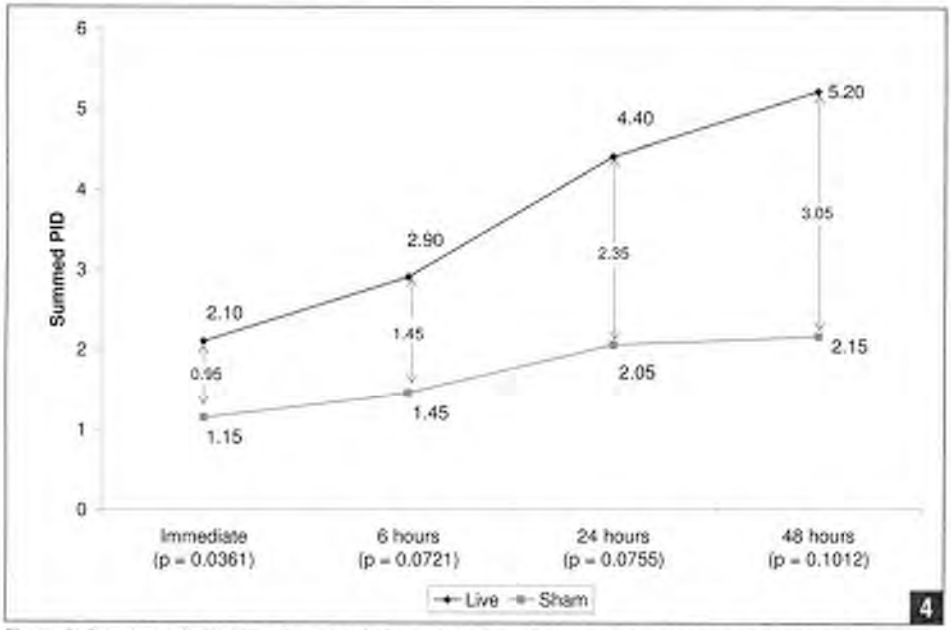

Figure 4: Summed pain intensity difference (values noted as centimeters on visual analog pain scale) for the live and sham groups.

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

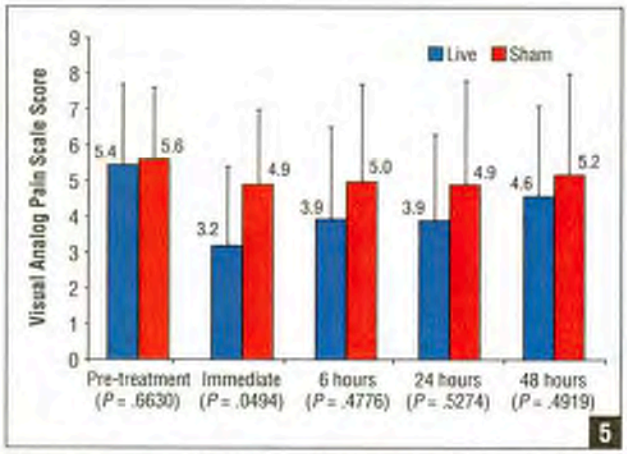

Figure 5: Raw visual analog pain scale scores recorded for live and sham groups. Significance is noted at the immediate post-treatment period.

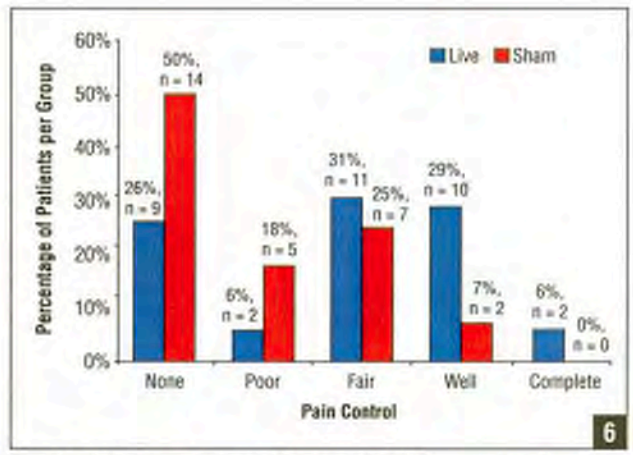

Figure 6: Distribution of pain control assessed at 48 hours post-treatment. The live group has significantly better pain control than the sham group ($P=.039$).

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

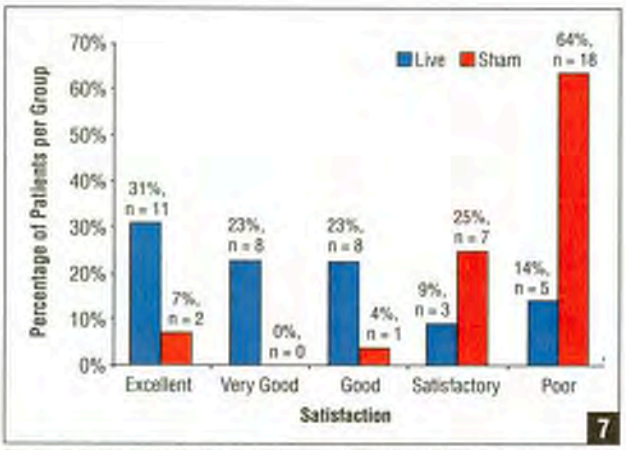

Figure 7: Patient satisfaction at 1-week post-treatment. Live group has significantly higher patient satisfaction than the sham group ($P<.0001$).

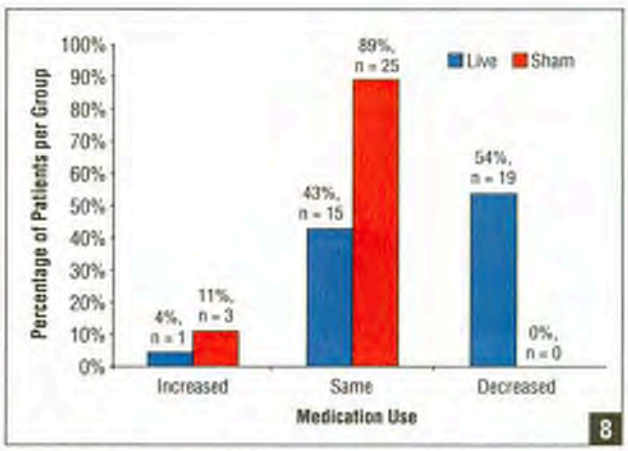

Figure 8: Medication use reported at the 1-week post-treatment. The live group had significantly less medication use ($P<.0001$) than the sham group.

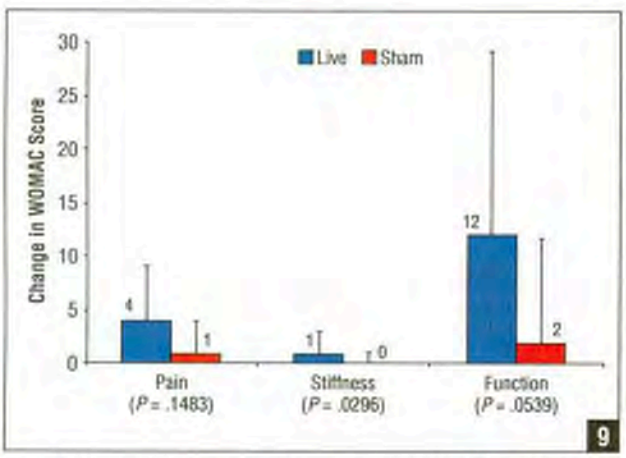

Figure 9: Change in WOMAC score from pretreatment to 48 hours post-treatment. The live group was statistically significantly different from the sham group for the stiffness assessment.

($P<.0001$) 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 ($\alpha = .05$). 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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