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 ("BiowavePRO® with Deepwave® Percutaneous Electrode Arrays") 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**

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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 is a new technology based on the theory of hyperpolarization for inhibiting pain transmission. A new device called the BiowavePRO® Neuromodulation Pain Therapy System utilizing this technology has been developed (Figure 1), 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 Deepwave® percutaneous electrode arrays ("PEAs") (Figure 2). PEAs are a microneedle based technology comprised of 1014 microneedles 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

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

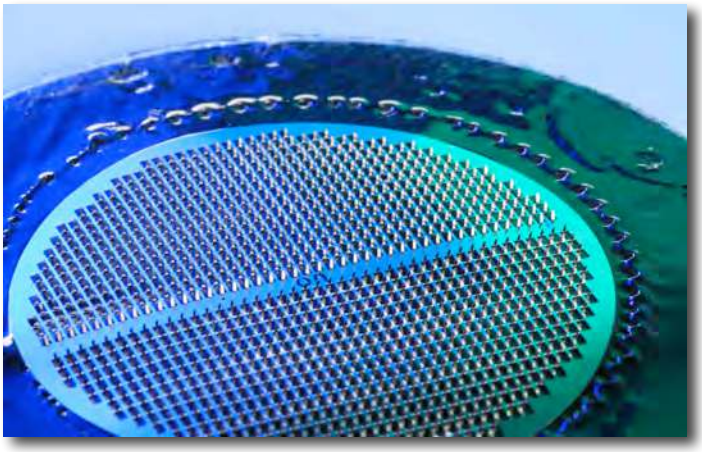

Figure 2

We hypothesize that the use of BiowavePRO® with Deepwave® 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

BiowavePRO® 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.

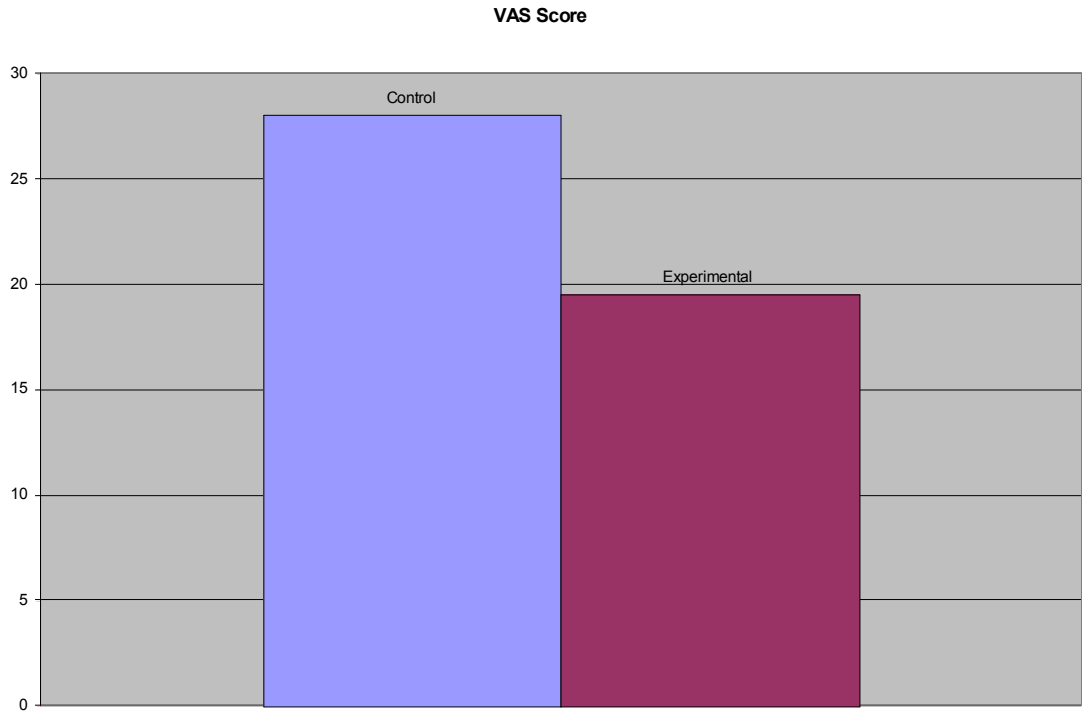

Figure 3: VAS Score

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 ($p = .09$).

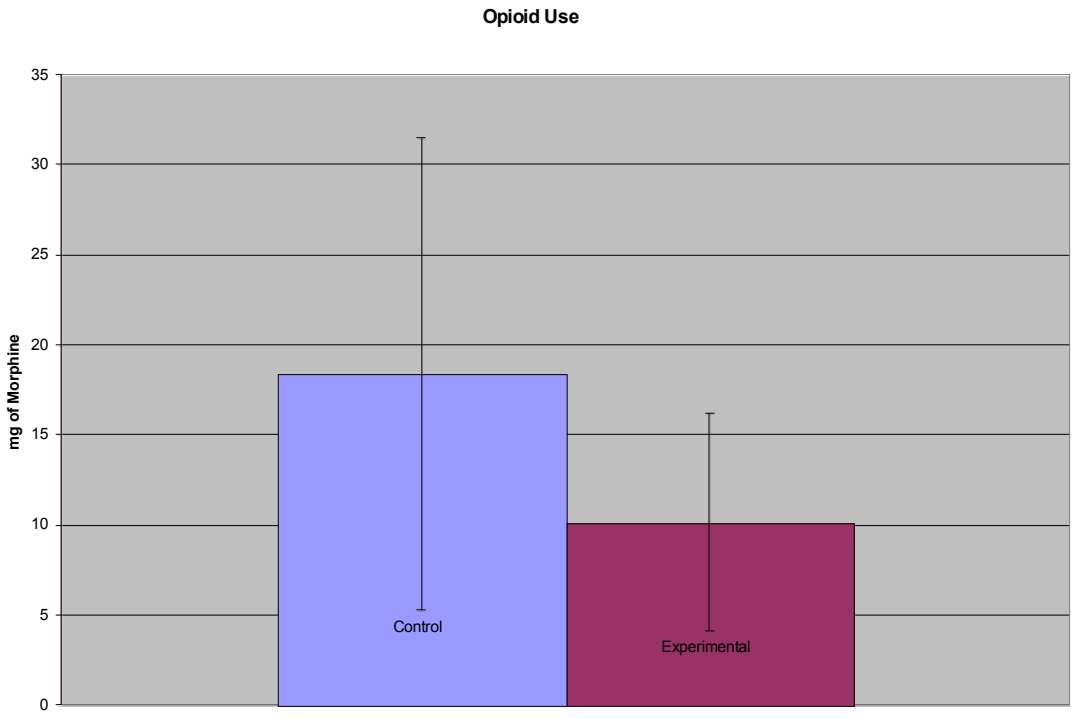

Figure 4: Opioid Use

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 BiowavePRO device incorporates a modification of TENS technology with the use of microneedles incorporated into a percutaneous electrode array which is thought to improve tissue penetration of the electrical signals while also creating a unique electric field with increased intensity. Based on results from this study, the BiowavePRO device appears to be effective in reducing the subjective measures of pain with a trend towards decreased opiod 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 BiowavePRO device. 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 BiowavePRO device 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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