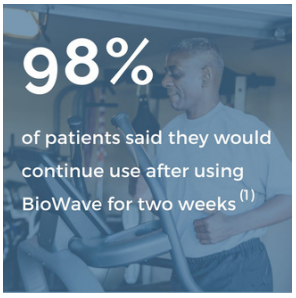
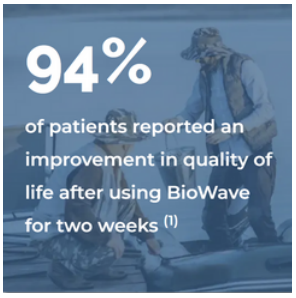
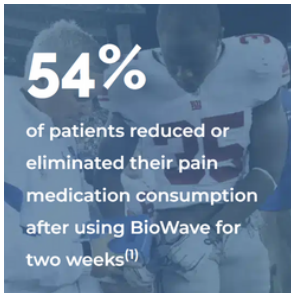
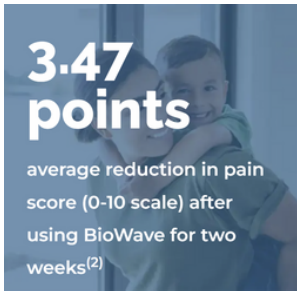
BIOWAVE
SMARTER PAIN BLOCKING TECHNOLOGY

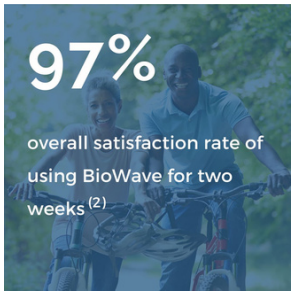
Clinical Studies

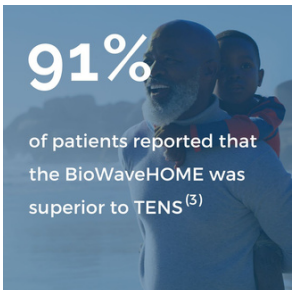


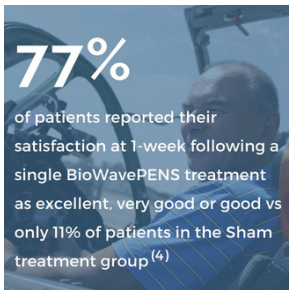












(1) Open Label Pilot Study Investigating Non invasive High-Frequency Peripheral Nerve Fiber Stimulation In Chronic Pain Patients. Outcomes from 463 study participants. © 2021 World Institute of Pain, Pain Practice, June 2021; 21(5):578-587

(2) Reduced Pain and Improved Function Following Short-Term Use of Noninvasive BioWave High-Frequency Peripheral Nerve Stimulation for Pain Management. Open-label survey of 1,511 chronic pain patients. Pain and Therapy, April 2023; 12(2):553-562
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(3) 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. Musculoskeletal Clinical Regulatory Advisors, White Paper, October 2017; 1-8

(4) Prospective Randomized Single-blinded Controlled Clinical Trial of Percutaneous Neuromodulation Pain Therapy Device Versus Sham for the Osteoarthritic Knee: A Pilot Study. Orthopedics, June 2007; 30(6):439-445

Updated date: 7.27.2023

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Reduced Pain and Improved Function Following Short-Term Use of Noninvasive BioWave High Frequency Peripheral Nerve Stimulation for Pain Management

Alaa Abd-Elsayed . Michael Gyorfi . Michael Fischman .
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Received: October 10, 2022 / Accepted: January 25, 2023

Pain Ther
https://doi.org/10.1007/s40122-023-00480-7

ORIGINAL RESEARCH

Reduced Pain and Improved Function Following Short-Term Use of Noninvasive BioWave High Frequency Peripheral Nerve Stimulation for Pain Management

Alaa Abd-Elsayed · Michael Gyorfi · Michael Fischman · Charles Odonkor · Bradford Siff · Kevin Cyr

Received: October 10, 2022 / Accepted: January 25, 2023

ABSTRACT

Introduction: The peripheral nervous system is an increasingly popular target for chronic pain treatment modalities. Noninvasive neuromodulation has shown promise at providing significant chronic pain relief with a much safer side effect profile. This retrospective pilot study is shaped around a noninvasive neuromodulation system over a 2-week treatment timeline.

Methods: Open-label survey of chronic pain patients recruited from Veteran Affairs, orthopedic, and pain health systems. If a noninvasive neuromodulation system was prescribed the patients were then offered a 2-week follow-up survey. This voluntary survey did not affect their therapy duration or quality. This survey was designed to address similar metrics as smaller noninvasive neuromodulation studies to allow a quality comparison while giving more power with a large population size of 1511 patients. Overall pain scores (including before and after scores), satisfaction level, desire to continue therapy, medication use, effect on functional metrics (mood, sleep, sit, stand, walk, and lift), and activities of daily living (ADL) scores were assessed.

Results: The results demonstrated an overall pain reduction of 46%. All functional metrics were improved throughout with the largest improvements reported in mood and sleep at over 47%. Medication use was reported as decreased or eliminated in 42% of patients. There were no adverse reactions or complications reported over the 1511 patients.

Conclusion: This survey is amongst the largest population sizes every studied for noninvasive neuromodulation. Within just 2 weeks patients can see a reduction in overall pain and medication needs. Although survey studies have inherent limitations such as duration and compliance biases with such an overwhelming benefit in every category we believe that noninvasive neuromodulation therapy is a promising, safe, and cost-effective therapy. Future studies should focus on long-term follow-ups

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Published online: 20 February 2023

and post-therapy pain scores with a placebo group.

Keywords: Noninvasive; Neuromodulation; Peripheral nerve stimulation; High frequency

Key Summary Points
Our study aimed at assessing the efficacy of non-invasive nerve stimulation using BioWave in treating chronic pain.
This was a survey study measuring pain scores before and after use of the device.
Study outcomes also included measurement of any adverse outcomes.
Out study concluded that this mode of therapy is effective.

INTRODUCTION

The prevalence of chronic pain continues to rise each year. A number of epidemiological studies done in various regions of the world found that chronic pain prevalence rates ranged from 12% to 80% depending on the country and demographic [1]. Chronic pain is often regarded as the most underappreciated healthcare issue affecting people's quality of life. In particular, chronic low back pain remains a difficult to treat clinical entity for which there is an unmet need for effective noninvasive interventions. The biological, psychological, sociodemographic, and behavioral effects of pain must all be considered when developing safe, preventative therapies [2].

The modern neuromodulation era began around the turn of the millennium, when a search for new therapies to effectively treat mental disorders with noninvasive, well-tolerated methods piqued interest, and studies on the influence of direct current on cerebral cortex excitability were pursued [3]. Electroconvulsive therapy (ECT), transcranial electrical stimulation (TES), transcranial magnetic stimulation (TMS), static magnetic stimulation, transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), random noise stimulation, ultrasound/focused ultrasound stimulation (FUS), and peripheral/cranial nerve stimulation are among the many noninvasive neuromodulatory techniques available today [4]. These technologies can be used to change brain circuitry for a number of therapeutic and non-therapeutic objectives, in addition to providing insight into our nervous system physiology.

The peripheral nervous system (PNS) provides a vital conduit of communication between the body and the environment. The PNS is an accessible window allowing physicians to manage both acute and chronic pain. Therapies that work via the PNS can be segregated into invasive techniques, including spinal cord stimulators, and noninvasive techniques such as transcutaneous electrical nerve stimulation (TENS) and PNS stimulators. This study focuses on the latter. The noninvasive neuromodulation therapy utilizes a high frequency electric field to bypass the skin's impedance. Two sinusoidal high frequency signals then penetrate deep tissues while a low frequency electric current spanning 1–180 Hz halts the action potentials' propagation. This creates a 4–6-cm region underneath the electrodes which is hypothesized to hyperpolarize the nearby C fibers. This hyperpolarization works via the frequency conduction block theory (FCBT) to inhibit the pain signals [5]. The principle of the FCBT is the multiplication of two sine waves that leads to the hyperpolarization of the C fibers (Fig. 1). The FCBT has parallels with the well-known gate control theory which targets the central nervous system and is utilized in spinal cord stimulators (SCS) [6].

Neuromodulation devices have proven to be a viable and safe alternative to traditional pharmaceutical therapies, with several studies demonstrating quality efficacy for migraine and cluster headaches [7].

Neuromodulation often uses either a tonic stimulation, where pulse signals are continuously fired over a set duration, or a more novel burst waveform pattern, where pulse signals are sent in rapid succession. The Neuromodulation

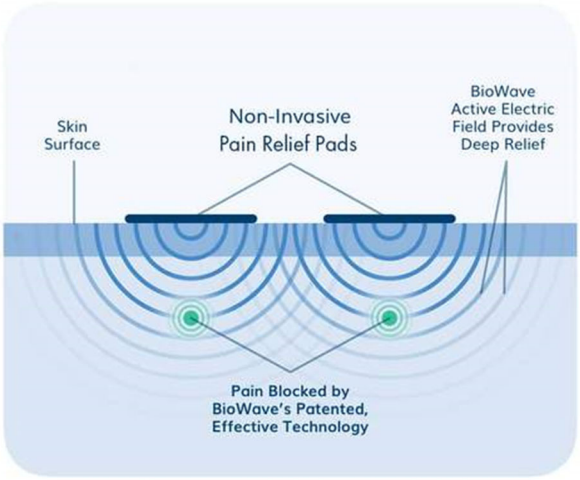

Fig. 1 Frequency conduction block theory

with BURST (SUNBURST) study was a randomized control study that demonstrated that burst stimulation was superior to the traditional tonic stimulation. The study indicated that patients preferred a treatment modality that was below the perception threshold [8].

TENS is a widely used noninvasive tonic neuromodulation treatment modality. The TENS nomenclature is based on the output of the device and not the physiological intention of the current. Conventional TENS selectively activates large diameter afferents via low intensity and low frequency signals typically in the range between 1 and 180 Hz. The intense TENS activates small diameter noxious afferents to elicit peripheral nerve blockade via high intensity and high frequency. TENS uses hyperstimulation and paresthesias to inhibit activity in the second-order nociceptive transmission [4, 9].

Noninvasive neuromodulators provide an alternative treatment modality for several acute and chronic pain conditions. These devices may offer a unique treatment flexibility since they may be employed as an early therapy, either alone or in conjunction with pharmaceutical treatment. Noninvasive neuromodulation is also a unique option for people in vulnerable patient groups, e.g., pregnant women and adolescents, as well as those who have had poor tolerability or effectiveness with pharmacologics [7–9].

Over the past 10 years the technology for PNS has advanced rapidly [10, 11]. For example, the first randomized control trial (RCT) that compared the efficacy of peripheral nerve field stimulation (PNFS) plus conventional medical management (CMM) vs CMM alone was in November 2012 when Medtronic Inc. performed the SubQStim II Study [12–15]. Neuromodulation now has several different leads and techniques that can be implemented for different subtypes of chronic pain.

We performed an open-label pilot study intended to add strength and depth to the current research of noninvasive burst neuromodulation effectiveness in people with chronic pain. A previous study of 463 individuals who were surveyed after 2 weeks of noninvasive neuromodulation therapy showed an average pain reduction of 3.05 points on a Numeric Pain Scale (NPS) [16]. This prompted follow-up studies with larger power to assess the efficacy of noninvasive neuromodulation therapy as a promising, safe, and cost-effective treatment modality.

METHODS

Participants

This pilot study was performed via retrospective review of volunteer surveys performed by patients with chronic pain primarily through Veterans Affairs (VA), pain centers, and orthopedic hospital systems over a 24-month period. The number of units shipped from January 1, 2021 through November 25, 2022 in the VA was 8779 and the number of surveys completed within the same time period for the VA was 1962. Therefore, the response rate is 22.4%. The majority of patients were male (66% of 1511 patients; Table 1). A wide variety of chronic pain subtypes were treated, the most common being back pain and neck pain (60% and 9%, respectively; Table 3). There were patients with more than one chronic pain location; however, the survey recorded the primary site of treatment. Those not able to understand English, and patients not capable of operating the noninvasive neuromodulation device were

Table 1 Patients' demographics

Demographic	Frequency	Percent
Male	993	66
Female	304	20
No gender response	214	14
VAMC	1203	79.6
Orthopedic center	236	15.6
Pain center	72	4.8
	Range (years)	**Mean**
Age	24–90	58.4 (± 13.9)

VAMC Veteran Affairs Medical Center

excluded. The subject of this study is a clinically tested at-home neuromodulation device called the BioWaveHOME (Norwalk, CT, USA: BioWave Corporation). This study was ethically sound and an institutional review board (IRB) waiver was obtained.

Each patient had a thorough noninvasive neuromodulation system demonstration where they learned the necessary skills to perform a standardized treatment and the 2-week survey was discussed. The patient's willingness to participate in the survey did not impact their quality or duration of care. After 2 weeks of noninvasive neuromodulation therapy the surveys were collected.

Questionnaire

A questionnaire was designed and tested the survey in conjunction with healthcare providers and patients from VA Hospitals. Mock-up surveys were created and refined several times incorporating both provider and patient feedback. The survey consisted of 15 questions: pain score reduction (with pre- and post-therapy scores), activities of daily living (ADL) score change (with pre and post scores), primary chronic pain location, change in quality of life (QoL), mood, desire to continue therapy, satisfaction level, medication use, and effects on functional metrics: mood, sleep, sit, stand, walk, and lift (Fig. 2). The activity of daily living score comes from a 10-point scale that assess hygiene, dressing, toileting, locomotion, continence, and meals. There was also an optional written section for patient comments and side effects. SPSS version 26 was used to perform the analysis which included descriptive analysis expressing data as numbers and percent. Pre- and post-intervention measures were presented as mean ± SD and compared using paired *t* test. A p value ≤ 0.05 was considered significant.

The patient treatment surveys were collected in several ways. The majority were received via mail followed by fax or email. Patients had the option to request phone surveys. In this scenario written consent from the provider to contact patients was obtained. Surveys were then entered into the electronic data collection system.

Noninvasive Neuromodulation

The BioWaveHOME system is a name brand noninvasive peripheral nerve stimulator. PNS stimulators are designed for temporary use and placement often occurs earlier in the perioperative setting. Devices are often removed between 14 and 60 days [11]. The systems consist of a control unit (Fig. 3a) and two types of electrodes. B-set electrodes (two 2-inch-diameter round electrodes) which are used in several fashions; two distinct areas of localized pain, origin and proximal pain location (radiculopathies), or one general area of pain (Fig. 3b). There is an alternative E-set electrode configuration, which is designed for treating a single location of pain. The E-set is comprised of a smaller 1.375-inch-diameter round electrode placed directly over the localized pain site; and a large 2 × 4 inch rectangular dispersive electrode that is placed over a bony prominence typically near the pain site, which is a comfortable location, to receive a deep soothing stimulation (Fig. 3c). The electrodes allow for the delivery of two high frequency sinusoidal signals to bypass the skin's impedance and penetrate deep tissues. Tissues that have a charge associated with them, like the membrane of the C fiber, act in a nonlinear fashion and force the multiplication of the two high

TWO WEEK SURVEY		
	1. Pre Pain Score	0-10
	2. Post Pain Score	0-10
	3. Pre ADL Score	10 point scale
	4. Post ADL Score	10 Point Scale
	5. Primary Chronic Pain Location	
	6. Change in Quality of Life	Improved, Unchanged, Worsened
	7. Improved Mood	True / False
	8. Desire to Continue Therapy	Yes / No
	9. Satisfaction level	0 -10 Score
	10. Medication use	Eliminated, Decreased, Unchanged, Increased
	11. Improved sleep	True / False
	12. Sit Longer	True / False
	13. Stand Longer	True / False
	14. Walk Further	True / False
	15. Lift More	True / False
	Comment Section (Optional)	

Fig. 2 Two-week survey example of 15 questions with answer options. Questions were mandatory apart from the comment section

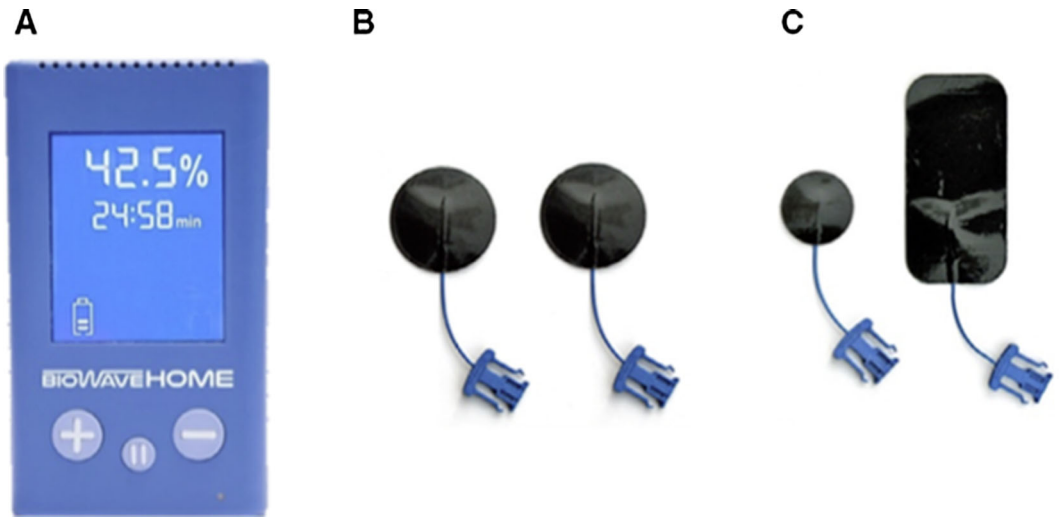

Fig. 3 BioWaveHOME control unit (**a**), B-set electrodes (**b**), and E-set electrodes (**c**)

frequency signals which results in the formation of a low frequency electrical field with current at 122 Hz, 4 kHz, 4.122 kHz, and 8.122 kHz that halt action potentials' propagation. This creates a 4–6-cm region underneath the electrodes which hyperpolarizes the nearby C fibers.

RESULTS

A total of 1511 participants completed surveys over the 24-month window; 66% were men while 20% were female and 14% did not indicate a gender (Table 1). The mean starting pain score was 7.56 with an average reduction of 3.47

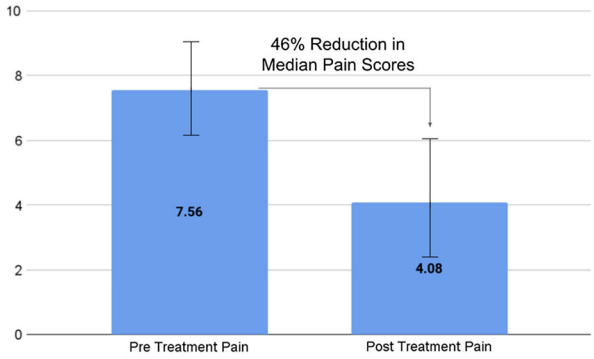

Fig. 4 Pre- and post-treatment pain scores

(Fig. 4). This was a statistically significant reduction ($p < 0.001$) in pain over a 2-week period (Table 2). A before and after ADL score demonstrated a vast improvement for most participants with the mean increase of 2.54 ($p < 0.001$) (Table 2).

The most common primary pain location among survey respondents was chronic back pain at 60%. This was followed by neck pain 9%, and ankle/foot pain 8% (Table 3). It is reported that 40–70% of patients with chronic pain report discomfort in more than one anatomical region so our survey recorded the primary site and treatment location [1].

Lifestyle metrics included quality of life (QoL), medication usage, and overall satisfaction rate. An improvement in QoL was reported by 87.6% of patients (Table 4). One-third of patients reported a reduction of medication while an additional 6% reported eliminating medication all together (Table 4). Patients were able to respond as eliminated, decreased, and unchanged medication use; 42% of patients reported that they were able to eliminate or reduce their medications and 39% reported no change in their medications. Overall, the non-invasive neuromodulation system satisfaction

Table 3 Primary location of chronic pain

Location	Frequency	Percent
Back	906	60
Neck	136	9
Ankle/foot	121	8
Knee	103	6.8
Hip	98	6.5
Shoulder	60	3.9
Sciatic/leg	44	3
Elbow	22	1.4
Wrist/hand	21	1.4
Total	1511	100

Table 4 Lifestyle metrics

Metric	# Improved	% Improved
Improved quality of life	1323	87.6
Medication reduction	552	36.5
Medication elimination	91	6

Table 2 Pain and ADL scores

Metric	Minimum	Maximum	Mean ± STD	Two-sided *p*
Pre pain score	3	10	7.56 ± 1.633	
Post pain score	0	10	4.08 ± 1.96	< 0.001
Pain score change	0	6 (reduction)	3.47 ± 1.95	
Pre ADL score	1	10	7.12 ± 1.97	
Post ADL score	0	10	4.08 ± 1.96	
ADL score change	0	8 (reduction)	2.54 ± 2.22	< 0.001

ADL activities of daily living, *STD* standard deviation

Table 5 Satisfaction

Metric	# Patients	% Patients
Desire to continue therapy	1469	97.2%
Desire to stop therapy	42	2.8%
	Mean score	
Satisfaction	8.35	

Satisfaction score on 0–10 scale where zero is not satisfied and 10 is completely satisfied

rate was 8.35 on a scale of 0–10 and 97.2% of patients wanted to continue therapy after completing the survey (Table 5).

Functional Outcomes

Functional outcomes, i.e., ability sit, stand, walk, and lift along with sleep and mood, were assessed. Patients were given the option of their ability to perform said tasks as improved, same, or decreased. There was an average improvement in all activities. Almost half of all patients reported sleep 47.9% and mood 47.7% being the most improved (Table 6).

DISCUSSION

This open-label pilot study demonstrated significant improvement for patients with chronic pain in several key areas: quantitative pain levels, activities of daily living, quality of life, medication usage, functional metrics, and overall satisfaction. It is worth noting that this unique bioelectronic therapy was able to produce these results in a time frame of just 2 weeks.

Table 6 Functional metrics

Metric	# Improved	% Improved
Sleep	724	47.9
Mood	720	47.7
Stand	671	44.4
Walk	655	43.3
Sit	617	40.8
Lift	268	17.7

Our survey had one of the largest population sizes of any PNS neuromodulation study with 1511 patients. This pilot survey demonstrated an overall satisfaction rate of 97% and an average pain reduction of 3.47. This is in line with previous studies of noninvasive high frequency neuromodulation [16]. Our study was able to provide a strong correlation with all metrics. Despite the potential for selection bias amongst the survey respondents, data with positive improvement across a large group of subjects suggests possible underlying efficacy. Combined with the safe and at-home nature of this therapy, these results highlight the potential for this emerging form of electrotherapy.

TENS is used in a wide variety of chronic pain subsets; however, its efficacy is controversial. A large randomized, sham-controlled pilot crossover trial compared TENS and a placebo TENS therapy and found that although TENS was safe it was unlikely to offer more analgesic effects than a placebo [17].

There are many similarities between the new noninvasive neurmodulation techniques and TENS machines. They are both small, portable, battery-operated devices that use electricity to treat pain in a noninvasive pattern. The main difference is the hypothetical ability of the new neuromodulation systems to use alternating currents to block the pain signals via hyperpolarization.

While the technical revolution in PNS proceeds apace, fundamental concerns of biophysical and therapeutic significance remain unanswered. For example, the importance of contact spacing and several independent current controllers, as well as the advantages of constant current versus constant voltage schemes, is unknown. The appropriate number or arrangement of leads for controlling back pain with unilateral or bilateral leg discomfort must be determined [18, 19].

Our survey's universal improvements were seen independent of the clinical subgroup.

With the majority of the patients in this survey comprising veterans, it is promising to see a new therapy demonstrate significant benefit for this at-risk population. To better assess chronic pain treatment in veterans a study that integrates post-traumatic stress disorder (PTSD) scores and parallel coping strategies paired with neuromodulation could show a synergistic relationship between treatment modalities.

A noninvasive treatment modality that has a large safety profile with the ability to be reversed has numerous advantages. Chronic pain can often develop after surgical procedures making patients more reluctant to undergo another invasive procedure. Having a treatment option that does not require an operation could help patient adherence and possibly lead to treating chronic pain earlier in its disease process [20, 21].

Our large pilot study of 1511 patients demonstrates that the alternating current of the noninvasive neuromodulation system has the potential to treat numerous types of chronic pain conditions. Follow-up studies should be conducted to assess length of chronic pain reduction after treatment has stopped. They should also randomize placebo, new noninvasive neurmodulation techniques, and TENS treatment groups. Placebo effects can account for up to 30% of pain improvement in this population which could be further delineated with a control group in future studies [9].

Surveys and survey-based studies have inherent limitations. Compliance is potentially biased when it requires effort to submit the survey which is more likely if one has been performing their treatments. It is difficult to assess dishonest questionnaire answers or to assess a respondent's potential agenda. Patients may not be aware of the importance of each answer and the nuances between question choices despite prior survey education.

Despite having one of the largest noninvasive neuromodulation study populations the patients surveyed were biased towards men and specifically those in the VA health systems. This is a specific limitation when the prevalence of both acute and chronic pain is higher among women than men, with 66% of elderly women reporting pain in the past 4 weeks vs 57% of elderly men [22].

A way to strengthen future surveys would be to increase the length of treatment and the addition of a period without treatment. This could be accomplished in a follow-up survey. Although our survey portrays a significant pain reduction in a short period of time we have no data to suggest its longevity at this time.

CONCLUSION

Noninvasive neuromodulation is a promising treatment strategy for various types of chronic pain. We performed one of the largest noninvasive neuromodulation studies with 1511 patients surveyed. Patients from orthopedic, chronic pain, and the vulnerable population in the Veteran Affair Health Systems demonstrated considerable improvement in multiple categories, including quantitative pain levels, activities of daily living, sleep, mood, and numerous functional data points. The findings of this study generally matched those of prior noninvasive neuromodulation device studies and noninvasive neuromodulation investigations, while also providing much-needed power and reproducibility. This pilot study helps highlight the potential benefits of novel noninvasive neuromodulation treatment modalities while calling for randomized trials comparing neurostimulation devices versus placebo and TENS.

ACKNOWLEDGEMENTS

Funding. funding was received for the publication

Authors' Contributions. Alaa Abd-Elsayed, MD, MPH, FASA: Study design, data analysis and manuscript writing. Michael Gyorfi, MD: Data analysis and manuscript writing. Michael Fischman, MD: Study design and manuscript writing. Charles Odonkor, MD: Study design and, manuscript writing. Bradford Siff: data

collection and manuscript writing. Kevin Cyr: data collection and manuscript writing.

Disclosures. Alaa Abd-Elsayed, Michael Fischman, Charles Odonkor are consultants fir BioWave, Bradfor Siff and Kevin Cyr have appointments with Biowave.

Compliance with Ethics Guidelines. This study was ethically sound and an IRB waiver was obtained from the University of Wisconsin.

Data Availability. The data sets generated during and/or analyzed during the current study are not publicly available due to the need for patient data protection and the lack of IRB permission to share it in public.

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An Open-Label Pilot Study Investigating Noninvasive High-Frequency Peripheral Nerve Fiber Stimulation in Chronic Pain

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Pain Practice, Volume, Issue, 2021

ORIGINAL ARTICLE

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■ **Abstract**

Objective: Providing sustained and effective treatment via the peripheral nervous system for the management of chronic pain is challenging. Application of noninvasive high-frequency stimulation at or near the painful area may benefit those with chronic pain. This open-label pilot survey examined the impact of this stimulation on pain intensity, activities of daily living, functional capacity, and medication consumption after 2 weeks of treatment.

Methods: Stimulation was administered at home using two high-frequency sinusoidal alternating signals at 3858 and 3980 Hz delivered between two electrodes placed directly over one or two locations of pain. Individuals completed a survey after 2 weeks to assess pain, activities of daily living (ADL), pain medication consumption, quality of life (QoL), mood, sleep, functional outcomes, and satisfaction.

Results: 463 individuals (372 males; 91 females) retuned the completed survey after 2 weeks of treatment. Pain and ADL scores significantly improved at follow-up compared with baseline (pain mean difference: 3.05; 95% confidence interval [CI]: 2.86, 3.24; ADL mean difference: 1.82; 95% CI: 1.60, 2.04). Corresponding improvements in QoL, sleep, mood, functional outcomes, and satisfaction were noted. On average, 8.00 ± 11.11 hours of pain relief were reported with 54% experiencing reductions in pain medication consumption. 98% would use the stimulation in the future.

Conclusion: Two weeks of noninvasive high-frequency peripheral nerve fiber stimulation appeared to confer positive effects in individuals with chronic pain. Future research employing a control group/arm is needed to establish the long-term impact of this bioelectric technique in specific pain cohorts. ■

Key Words: noninvasive, high frequency, peripheral nerve fiber stimulation, pain, activities of daily living

INTRODUCTION

The prevalence of chronic pain in the general population ranges from 35% to 51% in the U.K.[1] and from 19% to 43% in the U.S.A.[2] Chronic pain is recognized as a global health priority[3] and is characterized by severe pain continuing longer than 3 months despite medication or treatment.[4] It can negatively impact quality of life, sleep, physical mobility, employment, and mental health[5–9] and has economic implications.[10–12] Chronic pain is particularly prominent among former military personnel[13,14] and a contributing reason for medical discharge.[15] Indeed, it presents in 81.5% of veterans[16]

Submitted: October 27, 2020; Revised December 15, 2020; Revision accepted: December 17, 2020
DOI. 10.1111/papr.12993

and is closely tied to post-traumatic stress disorder (PTSD),[16–19] persistent postconcussive symptoms,[16] depression,[18,19] and alcohol misuse.[20]

The peripheral nervous system (PNS) offers clinicians the opportunity to treat both acute and chronic pain as it provides an accessible window into an integral pathway of communication between the body and the environment. Touch, proprioception, temperature, and nociception all influence our perception of the world. Pathological persistence of nociception from the PNS or peripheral nerve dysfunction can alter and amplify activity within pain pathways. This is termed peripheral sensitisation.[21,22] These pathophysiological sequences are driven by biochemical mediators that cause changes in the cell bodies of the somatosensory neurons which in turn can lead to central changes. Clinically, these changes result in ongoing pain, allodynia, hypersensitivity, or loss of function.[23]

At present, treatment options for chronic pain using the PNS may include physical therapy (eg, massage, desensitization, or acupuncture[24]), pharmacological management (eg, gabapentinoids, topicals, tricyclic antidepressants[25]), ablative therapy (thermal or chemical [24]), and/or neurostimulation (eg, spinal cord stimulation[26]). Recently, the term bioelectronic medicine applied to pain management has been used to describe the use of neurostimulation to modify the response of nerve tissue to reduce pain.[27] Examples include transcutaneous electrical nerve stimulation (TENS),[28,29] photobiomodulation,[30,31] and electromagnetic field,[32] all of which have been used in pain medicine. Bioelectronic medicine has an important advantage over other therapies, as it can employ electrical, magnetic, optical, and ultrasound technologies to deliver targeted, personalized therapy and eliminate the need for drug-centered therapy. The long-term objective is to improve clinical and economical outcomes.[33–35]

To have a meaningful sustained influence on the PNS, any noninvasive neuromodulation technology must bypass the impedance offered by the skin using a high-frequency electric field. It must also be able to provide a low-frequency electric field (1 to 180 Hz) to halt the propagation of action potentials that lead to the hyperpolarization required. This can be achieved by adding together two sinusoidal high-frequency signals, which pass into deep tissue and promote the further multiplication of these signals. This results in the formation of an active therapeutic low-frequency electrical field, focused in a 4- to 6-cm- (3.5-inch)-diameter hemisphere beneath and surrounding each electrode, not across the surface of the skin between the electrodes. This active electrical field is thought to hyperpolarize C-fibers inhibiting action potential propagation along these pain fibers (frequency conduction block theory). This technology is commercially available via a device called the BioWaveHome (BioWave Inc., Norwalk, CT, USA).

This open-label pilot survey was designed to quantify and understand the impact of this bioelectronic technology (BioWaveHOME) on individuals with chronic pain. The primary outcome measures were self-reported pain and activities of daily living (ADL). Secondary outcomes included medication consumption, quality of life (QoL), mood, sleep, physical function, satisfaction, and future usage. The study was exploratory to inform the protocols for future focused assessments.

METHODS

This was an open-label pilot survey that aimed to explore the efficacy of 2 weeks of BioWaveHOME in individuals with chronic pain in the U.S.A.

Participants

This was a retrospective review of anonymous data that were voluntarily returned by patients. Ethical approval was therefore not required. The therapy is a noninvasive treatment that is readily available in clinical practice. All adults who presented with a chronic lower-back, neck, upper- or lower-limb pain for more than 3 months were considered for inclusion. The individuals attended either a Veterans Affairs (VA) medical center, pain clinic, or orthopedic clinic between February 2019 and July 2020, where they were assessed by a healthcare professional for their suitability for treatment with a BioWaveHOME device as part of their treatment program. Some patients were treated with BioWavePRO during in-facility visits, while others were only provided the BioWaveHOME system for in-home use. Exclusion criteria included inability to read English and if the individual was not prepared to use the device consistently over a 2-week period. No a priori sample size calculation was conducted as responding to the survey was optional (see below for further details).

Treatment Protocol

All individuals were trained and advised on how to use the device and on the correct position of the skin pads.

The individuals were made aware of the option of responding to the voluntary and confidential evaluation survey within the first 2 weeks of use. Individuals were reminded this was optional and not a requirement of therapy. A prepaid envelope was provided. Data that were provided outside the 2-week initial treatment were not included in the final dataset.

Stimulation

Stimulation was delivered via the BioWaveHOME neurostimulator (BioWave, Norwalk, CT, U.S.A., see Figure 1A). A back-and-forth summation of two high-frequency sinusoidal alternating current signals at 3858 and 3980 Hz was administered. The current travelled between two electrodes which were placed directly over one or two locations of pain. The electrodes consisted of one of two types. B-set electrodes (see Figure 1B) were two 2.0-inch-diameter round electrodes for treating (1) two distinct locations of pain, (2) the origin of pain and most proximal location of pain to the origin (eg, in the case of a radiculopathy), or (3) one large area of pain (electrodes placed 1 inch apart from one another). E-set electrodes (see Figure 1C) comprised one 1.375-inch-diameter round electrode placed directly over a single location of pain and one 2-inch × 4-inch rectangular dispersive electrode placed over a bony prominence that was a comfortable location to receive stimulation. The stimulation elicited a deep, smooth sensation and was not in any way painful.

Data Collection

Figure 2 summarizes the study protocol. After 2 weeks of the stimulation, individuals were asked to complete a paper-based survey and return it via post. Briefly, the survey elicited responses on questions related to pain, ADL, medication consumption, QoL, sleep, functional outcomes, and satisfaction (see Table S1 for a summary of the survey).

Statistical Analysis

All statistical analyses were conducted in SPSS (version 25). Paired sample *t*-tests (or Wilcoxon signed-rank tests for non-normally distributed data) explored differences in pain and ADL between baseline and follow-up. Independent sample *t*-tests (or Mann–Whitney *U* tests) and one-way analyses of variance (ANOVAs; or Kruskal–Wallis tests) examined differences between groups. Normality was ascertained via the Shapiro–Wilk test, and all statistical tests were two-tailed. To control for multiple testing, the alpha level was adjusted using the Bonferroni correction. Change (Δ) between baseline and follow-up was calculated, and counts and percentages generated for categorical variables.

RESULTS

Demographics

In total, 463 individuals returned the survey over the 18-month period. There were 424 veterans (92%) and 39 members of the general public (8%). The predominant users were males (372 males; 91 females, see Table 1).

Most respondents suffered chronic pain alone with 21% reporting an acute pain during the 2-week period. Only a small percentage of the respondents were able to report the presence of different subtypes of pain (ie, neuropathic vs. nociceptive pain). Of the reported cases (n = 365), chronic back pain and chronic neck pain were reported in 295 respondents (81%). In general, pain in the periphery accounted for the remainder of the indication, but some overlap was noted (see Table 1 for a summary).

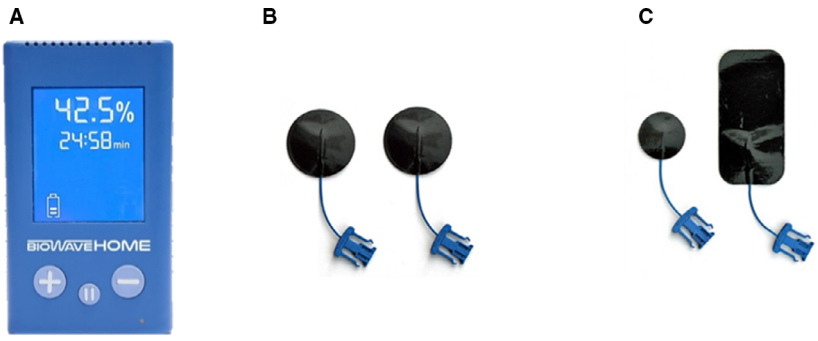

Figure 1. BioWaveHOME unit (A), B-set of electrodes (B), and E-set of electrodes (C).

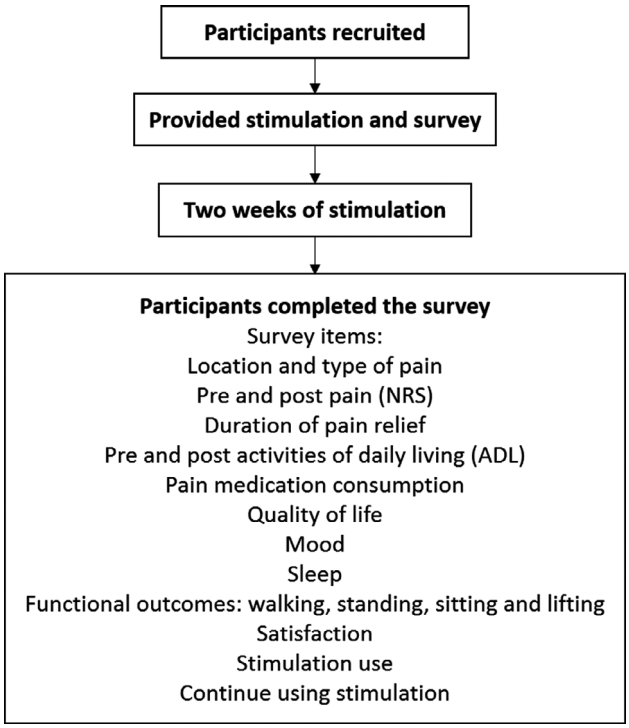

Figure 2. Summary of study protocol. ADL, activities of daily living; NRS, numerical rating scale.

Table 1. Summary of Characteristics of the Final Sample and Subgroups of Veterans and General Public

	Final Sample (n = 463)	Veterans (n = 424)	General Public (n = 39)
Gender			
Males	80%	83%	51%
Females	20%	17%	49%
Type of pain			
Chronic	91%	91%	97%
Acute	21%	22%	6%
Neuropathic	24%	23%	26%
Nociceptive	3%	3%	6%
Missing data (n)	37	32	5
Location of pain			
Back	70%	71%	69%
Neck	23%	24%	17%
Shoulder	25%	25%	20%
Ankle and/or foot	8%	8%	14%
Hand	2%	2%	9%
Leg, including sciatica	14%	15%	9%
Knee	16%	15%	17%
Missing data (n)	98	94	4

Data are presented as percentage apart from missing data which are presented nominally.

In the first 2-week period, survey responses revealed that just over half of the sample (51%) used the treatment daily, with 30% using the stimulation multiple times per day. The remaining participants reported using the treatment weekly (18%).

Pain and ADL Scores After 2 Weeks of Treatment

After 2 weeks of treatment, respondents reported an average reduction in pain of 3.05 (2.04) points. Pain was significantly lower following 2 weeks of treatment compared with baseline (mean difference: 3.05; 95% confidence interval [CI]: 2.86, 3.24; z-score = −17.37, $P < 0.001$, $r = 0.81$; Figure 3A). The average duration of pain relief reported by participants was 8.02 (11.11) hours (95% CI: 7.01, 9.04 hours).

Respondents also reported an average reduction in ADL scores of 1.82 (2.44) points following 2 weeks of the treatment. Compared with baseline, ADL scores were also significantly improved (mean difference: 1.82; 95% CI: 1.60, 2.04; z-score = −12.88, $P < 0.001$, $r = 0.60$; Figure 3b).

Intergroup analysis (ie, veterans, members of the general public) showed that significant improvements were seen in both pain and ADL scores. These improvements were universally noted across the multiple clinical indications (ie, pain types and pain locations, see Figures S1 to S5).

QoL, Mood, and Sleep

Improvements were also noted in the secondary outcome measures including QoL, mood, and enhanced sleep patterns (94%, 29%, and 33%, respectively, see Table S2).

Intergroup analysis (ie, veterans, members of the general public) showed the percentages of respondents reporting improvements in QoL, mood, and sleep were comparable in both groups. These improvements were also universally noted across the multiple clinical indications (ie, pain types and pain locations, see Table S2).

Respondents who reported improvements in QoL, mood, and sleep showed greater improvements in pain and ADL scores compared with those who reported little improvement in functional outcomes (see Tables 2 and 3).

Functional Outcomes

Improved functional capacity was reported by respondents. For example, 7% (33 of 463) could "lift more," 25% (115 of 463) could "sit for longer durations," 27% (125 of 463) could "walk farther," and 29% (133 of 463) could "stand for longer periods" of time (see Table S3).

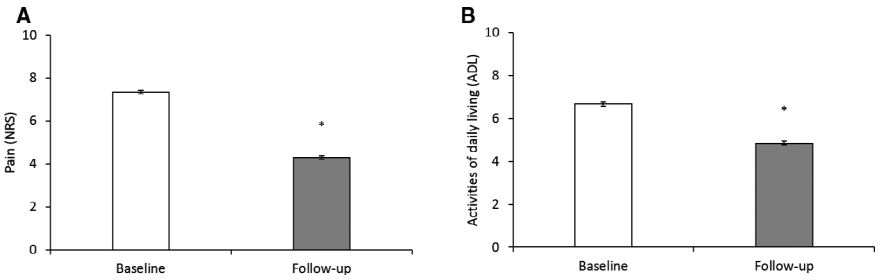

Figure 3. Pain (A) and ADL (B) scores during baseline and follow-up in the final sample. *Significantly different to baseline ($P < 0.001$). ADL, activities of daily living; NRS, numerical pain rating scale. Data are presented as mean ± 1 standard error of the mean (SEM).

Table 2. Summary of Differences in Improvements in Pain Scores Between Those Who Did and Did Not Report Improvements in QoL, Mood, and Sleep

	Pain Score				
	Z-Score	*P* Value	*r*	Mean Difference	95% CI
QoL	−5.25	< 0.001	0.25	2.19	1.40, 2.98
Mood	−3.01	0.003	0.14	0.68	0.27, 1.09
Sleep	−4.56	< 0.001	0.21	0.94	0.58, 1.31

CI, confidence interval; QoL, quality of life.

Table 3. Summary of Differences in Improvements in ADL Scores Between Those Who Did and Did Not Report Improvements in QoL, Mood, and Sleep

	ADL Score				
	Z-Score	*P* Value	*r*	Mean Difference	95% CI
QoL	−2.97	0.003	0.14	1.12	0.15, 2.09
Mood	−7.74	< 0.001	0.36	1.91	1.49, 2.33
Sleep	−9.22	< 0.001	0.43	2.15	1.75, 2.54

ADL, activities of daily living; CI, confidence interval; QoL, quality of life.

Intergroup analysis (ie, veterans, members of the general public) showed the percentages of respondents reporting improvements in functional outcomes were comparable in both groups. These improvements were universally noted across the multiple clinical indications (ie, pain types and pain locations, see Table S3).

Respondents who reported improvements in functional outcomes showed greater improvements in pain and ADL scores compared with those who reported little improvement in functional outcomes (see Tables 4 and 5).

Medication Consumption

The specific medication regime for each respondent was not recorded by the survey. The respondents were asked to report their oral medication consumption in one of three categories: "eliminated," "reduced," (ie, > 30%), or "stayed the same."

54% of respondents reported pain medication consumption was "reduced after treatment." In a small number of participants, 5% (21 of 405), pain medication was eliminated. Two of every five respondents reported medication consumption stayed the same in the 2 weeks of treatment.

Differences in change (Δ) in pain emerged according to type of change in pain medication ($H = 29.24$, $P < 0.001$, see Figure 4A). For respondents who reported pain medication consumption had been eliminated, they showed significantly greater reductions in pain compared with those who reported consumption had reduced (mean difference: −0.96; 95% CI: −2.17, 0.25; $P = 0.034$) or stayed the same (mean difference: −1.76; 95% CI: −2.98, −0.53; $P < 0.001$). Furthermore, pain relief was significantly greater for participants who reported reductions in pain medication consumption compared with those who stated consumption had stayed the same (mean difference: −0.80; 95% CI: −1.34, −0.25, $P < 0.001$).

There were no significant differences in change (Δ) in ADL scores between those who reported pain medication consumption had been eliminated, reduced, or stayed the same ($H = 1.82$, $P > 0.05$, see Figure 4B).

Table 4. Summary of Differences in Improvements in Pain Scores Between Those Who Did and Did Not Report Improvements in Functional Outcomes

	Pain Score				
	Z-Score	*P* Value	*r*	Mean Difference	95% CI
Lift	−3.51	< 0.001	0.16	1.25	0.54, 1.97
Sit	−2.86	0.004	0.13	0.70	0.27, 1.13
Walk	−6.07	< 0.001	0.28	1.31	0.91, 1.72
Stand	−4.64	< 0.001	0.22	1.02	0.62, 1.42

CI, confidence interval.

Table 5. Summary of Differences in Improvements in ADL Scores Between Those Who Did and Did Not Report Improvements in Functional Outcomes

	ADL Score				
	Z-Score	*P* Value	*r*	Mean Difference	95% CI
Lift	−4.58	< 0.001	0.21	2.02	1.18, 2.87
Sit	−6.73	< 0.001	0.31	1.71	1.27, 2.15
Walk	−8.49	< 0.001	0.39	2.10	1.68, 2.52
Stand	−8.62	< 0.001	0.40	2.08	1.66, 2.50

ADL, activities of daily living; CI, confidence interval.

Individual Satisfaction Scores

Overall, the level of satisfaction with the treatment was high with a mean score of 8.12 (1.84); where 0 was not satisfied and 10 was completely satisfied. For analysis, satisfaction scores were grouped into one of three bands (1 to 4, 5, or 6 to 10). Change in pain and ADL scores significantly differed between the three satisfaction groups ($H = 27.66$, $P < 0.001$ and $H = 8.08$, $P = 0.018$, respectively, see Figure 5). Respondents scoring 6 to 10 had significantly greater improvements in pain and ADL compared with those scoring 1 to 4 for satisfaction (pain mean difference: −2.12; 95% CI: −3.11, −1.12, $P < 0.001$; ADL mean difference: −0.98; 95% CI: −2.20, 0.25, $P = 0.042$).

Most respondents (98%, 449 of 460) stated they would continue using the stimulation after the 2-week period. Four participants reported indifference towards future usage, while seven said they would not continue with the stimulation. Data concerning future usage was missing in three instances. Similar patterns were observed across all subgroups (see Table S5).

DISCUSSION

The key findings of this article suggest that the noninvasive high-frequency neuromodulation used here can (1) significantly improve pain intensity and ADL and (2) positively impact QoL, mood, sleep, and functional outcomes following 2 weeks of treatment. The ability of this novel bioelectronic therapy to achieve these outcomes in such a short timeframe is a noteworthy observation. Respondents also reported high levels of satisfaction, and 98% of participants stated they would continue using the treatment. These findings are novel and timely, providing the initial evidence base needed to further assess this treatment's efficacy in chronic pain at a time when there is demand for pain treatments that are safe and cost-effective.

Noninvasive High-Frequency Neuromodulation in Pain

As chronic pain is characterized by increases in central and peripheral nerve activity,[36] electrical stimulation of the PNS may offer an alternative and effective way for reducing this hyperactivity. Noninvasive bioelectronic medical therapies, such as TENS,[28,29] photobiomodulation,[30,31] and electromagnetic field,[32] have been trialed in pain conditions to mixed effect. This pilot survey aimed to evaluate the impact of using a noninvasive neuromodulation device that can deliver high-frequency electrical stimulation to peripheral nerve fibers as a treatment option for chronic pain. Findings point to the benefits this stimulation can have on pain, ADL, QoL, mood, sleep, and physical ability after 2 weeks of use. Evidence from animals (see Ref. 37 for a review) suggests that high-frequency (kilohertz) nerve conduction blocks facilitate rapid, reversible, and localized blocks of nerve conduction. The stimulation employed in this study is based on the principle of a multiplication of two sine waves (ie, a Fourier Transform). In terms of potential mechanism of action, the electrical field generated from this stimulation may lead to hyperpolarized C-fibers, in

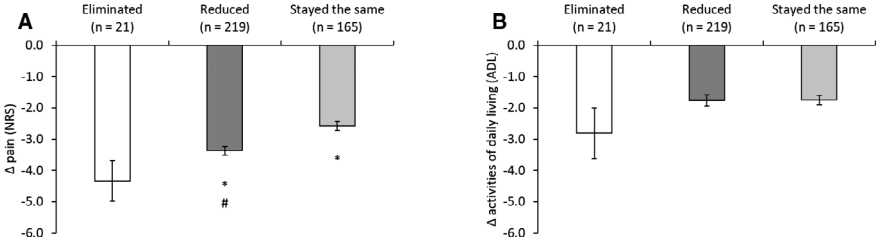

Figure 4. Change (Δ) in pain (A) and ADL (B) scores for participants who reported pain medication consumption had been eliminated, reduced, or stayed the same following 2 weeks of stimulation. *Significantly different to "eliminated" ($P < 0.05$); #Significantly different to "stayed the same" ($P < 0.001$). ADL, activities of daily living; NRS, numerical rating scale. Data are presented as mean ± 1 standard error of the mean (SEM).

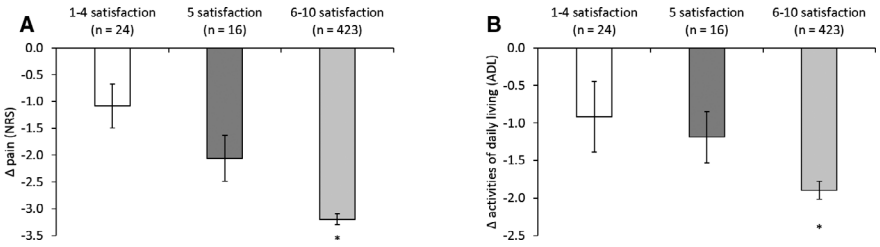

Figure 5. Change (Δ) in pain (A) and ADL (B) scores for participants who reported 1 to 4, 5, and 6 to 10 for satisfaction with the stimulation. *Significantly different to 1 to 4 satisfaction ($P < 0.05$). ADL, activities of daily living; NRS, numerical rating scale. Data presented as mean ± 1 standard error of the mean (SEM).

turn inhibiting action potentials from propagating along the pain fibers and therefore reducing pain sensations.

We acknowledge the design of this pilot survey was not perfect and that caution is needed when interpreting and generalizing the reported findings. However, the data were robust, given that findings consistently pointed to a relationship between improvements in pain and ADL when compared with baseline (pretreatment scores) and between groups after the treatment had taken place. Intriguingly, these improvements were correlated with improvements in a number of secondary outcomes, including QoL, mood, sleep, functional outcomes, medication consumption, and satisfaction with the treatment. Further research is needed to see whether these relationships can be extended beyond the initial 2-week treatment.

It is interesting to note that the observed improvements can be achieved with relatively little effort on the part of the individual. On average, two treatments per day, each lasting 30 minutes, are recommended in the initial stages of treatment. We found that 80% of respondents adhered to this regime. The average duration of relief reported was 8 ± 11 hours. This would therefore suggest that respondents found the requirement to commit to two 30-minute sessions each day, and this may have provided them with a sense of improvement to justify this commitment. We recognize that compliance was high among those who returned the survey. It is possible that improvements were noted as respondents had a focused plan for treatment and were motivated by the short-term goals. As this study was open-label, future research should employ a valid control to test the robustness of the findings. Although, a possible placebo effect may explain 30% improvement in pain and ADL, it would not explain the consistent improvements across all outcomes when the data were cross-analyzed.

Intergroup Analysis

The improvements reported in this pilot survey were independent of the clinical subgroups and the source of the chronic pain. Pain beliefs and coping strategies play a key role in modulating QoL and pain.[38] These modulatory effects are particularly strong in veterans, especially in those in whom chronic pain and PTSD are comorbid.[15,39] This sample comprised mainly veterans ($n = 424$) with findings showing that outcomes improved following 2 weeks of noninvasive high-frequency stimulation. Having a treatment that may offer this cohort a treatment option is an advantage. We recognize that the comorbidity of PTSD was not ascertained in this study rendering it unclear to what extent PTSD influenced responses to the noninvasive high-frequency peripheral nerve fiber neuromodulation. To better target treatment for this group, future research should assess for PTSD and pain coping strategies. Although there is little evidence to suggest that veterans suffer chronic pain differently than an individual who has not served in the armed forces,[40] the cause of the pain may be different (eg, polytrauma), military recruits may be drawn from a particular section of the population, and they may bring their own characteristics and comorbidities.[15]

As the sample comprised mainly veterans with males being the predominant gender in veteran groups,[41] the resulting sample had a minority of females. In the general population, the existence of gender differences in pain perception, pain severity, and response to analgesic treatment is acknowledged.[42] In veteran samples, there also seems to be differences between males and females in the prevalence, health care utilization, and severity of chronic pain.[43–46] Therefore, the role gender plays in modulating the magnitude of improvement in outcomes to noninvasive high-frequency peripheral nerve fiber stimulation in veterans should be explored in future research. This can be achieved by

enlarging the cohort to include additional centers. The inability to classify the nature of the pain (neuropathic or nociceptive) resulted from the fact that the information was collected independently of medical input. Therefore, future research investigating the effects of chronic pain treatments in veterans should carefully take these factors into account.

Survey Limitations and Areas of Improvement

The survey design fulfilled the key objectives as a preliminary assessment tool. This simple survey was designed with the objective of having 12 questions or less and taking less than 5 minutes to complete in a paper format. The average response using a coordinated multimedia approach to any survey would be 30% when a combination of survey techniques, such as in-patient survey, online, direct email correspondence with the option of reminders, telephone calls, and/or app questionnaire, are used.[47] Although this level of data collection was not used in this pilot survey, the paper format was able to return enough clinically relevant data. Indeed, the completed survey set was high, ensuring the data recovered were of high quality. Also, statistical analysis established clinically significant improvements in the primary outcomes, which were associated with improvements in the secondary outcomes.

A digital marketing strategy could be used in future studies (eg, personalized text messages/emails, etc.). This would allow for an extension to the follow-up period and facilitate real-time data collection, providing added value. The data collected in this survey has generated the knowledge to design the long-term assessment plan that is required to evaluate this treatment. We accept that some aspects including the nature of the pain (acute, nociceptive, or neuropathic) and the analgesics used depended on the subjective report of individuals and could be improved. These aspects will be included in the next phase assessment. It is hoped that by extending the follow-up duration, including a control group, improving the mode of data collection, and ascertaining medication use (eg, opioid use) and pain diagnosis from medical professionals, data quality will be enhanced.

CONCLUSIONS

This open-label pilot survey highlighted the potential role of a novel bioelectronic technique to manage pain and improve ADL. With further research comparing the longer-term effects of this stimulation with a control arm/group in specific pain cohorts, the efficacy of noninvasive high-frequency neuromodulation in pain will become more established.

ACKNOWLEDGEMENTS

We would like to thank all of the individuals who gave their free time to reply to the survey.

CONFLICT OF INTEREST

In the past, D.H. has received speaker honorarium from Platform 14 to participate in cadaver workshops in the area of peripheral nerve stimulation techniques. B.B. has provided consultancy on medical writing and data analysis to Platform 14.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Summary of Survey Items.

Table S2. Participants Who Did and Did Not Encounter Improvements in Quality of Life, Mood, and Sleep.

Table S3. Participants Who Did and Did not Encounter Improvements in Functional Outcomes Including Lifting, Sitting, Walking, and Standing.

Table S4. Participants Who Reported Pain Medication Had been Eliminated, Reduced, or Stayed the Same After 2 Weeks of Treatment.

Table S5. Participant Satisfaction with the Stimulation and Future Use.

Figure S1. Pain (A) and activities of daily living (ADL) (B) scores during baseline and follow-up for the group of veterans and members of the general public.

Figure S2. Pain during baseline and follow-up in participants who reported chronic, acute, neuropathic, and nociceptive pain.

Figure S3. Pain during baseline and follow-up in participants who reported pain in the back, shoulder, neck, knee, leg, and ankle and/or foot.

Figure S4. Activities of daily living (ADL) scores during baseline and follow-up in participants who reported chronic, acute, neuropathic, and nociceptive pain.

Figure S5. Activities of daily living (ADL) scores during baseline and follow-up in participants who reported pain in the back, shoulder, neck, knee, leg, and ankle and/or foot.

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August 2020

MCRA Whitepaper

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White Paper

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ABSTRACT

Introduction: To date, more than 750,000 people in the United States alone have died from a drug overdose, with two out of every three overdose deaths in 2018 involving the use of opioids. In 2019 alone, the estimated cost of the opioid epidemic was reported at $179.4 billion, with $72.6 billion attributed to overdose deaths and $60.4 billion attributed to related healthcare costs [1]. Veterans, who are more likely to suffer from chronic pain and post-traumatic stress disorder (PTSD) than civilians, are twice as likely to die from an opioid addiction. With opioids as one of the most commonly utilized methods of pain management, it is not surprising that opioid addiction and overdose among Veteran populations has increased in recent years, creating a dire need for non-pharmacological, non-invasive, and non-addictive conservative treatment alternatives. The BioWaveHOME system provides an alternative to opioid pain management through electrical field generation inside the body, potentially addressing this unmet medical need.

Methods: From the period of February 2019 through July 2020, 6,245 subjects received a BioWaveHOME for at-home pain management on an as-needed basis for a minimum of two weeks, with some subjects receiving in-facility prior treatment with the BioWavePRO system. With the BioWaveHOME, subjects were provided with a mail-in survey to record pre-and post-treatment pain (Numeric Rating Pain Scale (NRS)), change in activities of daily living (ADL Scale) following treatment with the BioWaveHOME system, and other subject-reported outcomes, including satisfaction and quality of life, following two weeks of use. Also evaluated was change in pain and ADL based on anatomic region.

Results: Following two weeks of BioWaveHOME use, four hundred sixty three (463) subjects provided responses via returned surveys. The BioWaveHOME device provided subjects with statistically and clinically significant reductions in pain, with an average reduction in pain score of 3 points. Most subjects that initially reported pain localized to the back (n=257) reported an improvement in pain score of 3, with patients reporting pain localized to the hip (n=39), knee (n=57), and shoulder, (n=91) reporting an improvement in pain score of ~3.5 points. Further, the majority of subjects (87.7%) reported that using the BioWaveHOME improved their quality of life. With regard to activities of daily living, subjects reported significant improvement following use of the BioWaveHOME, with an improvement of 1.8 points. Analysis by anatomy revealed that all anatomies fared similarly with regard to improvement in ADL, with all reporting an improvement of around 1.8 to 2 points. With most subjects reporting daily use of the system, the average period of relief provided after each use was reported as eight (8) hours. Importantly, more than half (51.8%) of subjects reported either eliminating or reducing pain medication consumption while using the BioWaveHOME system. Patient satisfaction was particularly high, with the majority of subjects (97%) reporting being satisfied with the BioWaveHOME system with an expressed desire to continue using the system. All subjects were reported to have continued use of the BioWaveHOME device after the two-week recording period. Overall, use of the BioWaveHOME for two weeks on an as-needed basis resulted in substantial improvement in quality of life and reduction in pain for patients suffering from chronic and acute pain.

INTRODUCTION

According to the most recent dataset from the Center for Disease Control (CDC), approximately 50 million adults in the United States suffered from some form of chronic pain in 2018, up from 20 million adults in 2016 [2]. Further, greater than 19.6 million chronic pain sufferers categorize their pain as "high impact," defined as physically-limiting, debilitating pain lasting for greater than six months. Chronic pain has been reported as one of the most common reasons adults seek medical care, linked to restrictions in mobility and activities of daily living, substance abuse, anxiety, and depression.

A higher prevalence of chronic pain has been observed in older populations, correlated to advancing age and the female gender [2]. Former military personnel have also been linked to high rates of chronic pain, with a recent study conducted by the Veterans Health Administration reporting that 47-78% of Veterans presenting to VA clinics for care were seeking treatment for some form of persistent pain [3].

While there is currently no definitive "gold standard" treatment for chronic pain, prescription opioids are one of the most commonly utilized methods of care. While satisfactory in the short-term, the prolonged use needed to allay chronic pain has devolved into an epidemic of widespread misuse and a 2017 public health emergency declaration by the Department of Health and Human Services. In 2018, it was reported that an estimated 10.3 million Americans were misusing opioids, with two million of these adults actively seeking treatment for opioid use disorder. The National Institute for Drug Abuse estimated that opioid overdose takes the lives of 130 people each day, further underscoring the significance of this epidemic [4]. The predominance of chronic pain among Veteran populations is particularly concerning, as studies have demonstrated former military personnel are ten times more likely to become addicted to opioids and two times more likely to succumb to opioid addiction than the general population due to an increased rate of psychiatric comorbidities, such as PTSD [5].

With an aging population and prevalence of chronic pain on the rise, the public health burden of pain and opioid addiction is becoming exponentially more costly. In 2019 alone, opioid addiction cost the United States $179.4 billion, with $72.6 billion attributed to overdose deaths and $60.4 billion attributed to healthcare costs [1]. To combat this, alternative treatments are being actively sought while physicians attempt to decrease the number of opioid prescriptions written. From 2009 to 2011, 50% of chronic non-cancer pain Veterans treated within the VA health system received an opioid prescription. In 2016, the number of opioid prescriptions within the VA health system decreased by 25% [6]. While encouraging, non-prescription opioid use is largely unregulated and, as such, long-term use of opioids still remains an issue with the general and veteran population.

One promising treatment avenue that presents a non-addictive, non-pharmacological therapy to pain sufferers is the use of transcutaneous electrical nerve stimulation therapies, commonly referred to as TENs units. The technology is such that low-dose, non-invasive electrical current stimulates vibration receptors in the area treated for pain, reducing the transmission of painful stimuli to the brain. Repeat use results in the release of endogenous endorphin, contributing to the reduction in pain [7]. TENs technology works to mask the pain, providing short-term relief. The limitation of TENs technology is that the pain signals are not blocked, only masked. Using a novel patented electrical signal technology, BioWave Corporation has developed the BioWavePRO and BioWaveHOME neurostimulation systems for in-office and in-home pain relief, respectively. Both systems have been cleared by the FDA for use, with BioWavePRO cleared for physician use in 2005 and BioWaveHOME cleared for in-home use in 2015.[1]

A 2017 white paper reviewing the use of the BioWavePRO and BioWaveHOME systems in 66 surveyed veterans over the course of 18-months reported that 84.8% of all subjects experienced a reduction in pain, increased range of motion, and improved participation in activities of daily life. Of note, 58.7% of the surveyed veterans reported eliminating or reducing consumption of prescription pain medication since beginning treatment with the BioWaveHOME [8]. To further understand the impact of BioWaveHOME as a pain relief intervention and its impact on a patient's activity of daily living, additional patients should be evaluated.

PURPOSE

The objective of this study is to evaluate the use of the BioWaveHOME system in 463 surveyed subjects, including both Veterans and members of the general population, suffering from chronic or acute pain. The outcomes collected from returned surveys include pre- and post-treatment pain and activity, frequency of use, change in concomitant pain medications, satisfaction with the treatment, and other subject-reported quality of life outcomes.

MATERIALS/METHODS

Eligible subjects were provided with the BioWaveHOME System for pain management

[1] BioWavePRO – K052289; BioWaveHOME – K152437

following treatment at either a VA Medical Center, pain clinic, or orthopedic clinic. Some patients were treated previously with BioWavePRO during in-facility visits while others were only provided the BioWaveHOME system for in-home use. Accompanying the unit was an optional survey to complete following two weeks of continued use. Of the 6,245 subjects provided with the BioWaveHOME device, 463 provided fully or partially answered surveys back to BioWave, Inc. (7.4% response rate). Survey responses were mostly received following two weeks of use of the BiowaveHOME, though some responses were submitted to BioWave later. The dataset includes surveys returned from February 2019 through July 2020.

The survey was intended to capture responses after two weeks of BioWaveHOME use. Subjects were asked to record the following:

- **Description of Pain**: *Subjects were asked to detail their pain, inclusive of anatomic area.*
- **Type of Pain**: *Subjects were asked to check a box correlated to type of pain: chronic, acute, neuropathic, and/or nociceptive in nature.*
- **Pre-Treatment and Post-Treatment Pain Evaluation**: *Subjects were asked to circle a number on an NRS scale of 0 (no pain) to 10 (worst pain), correlated to the Wong-Baker Faces scale.*
- **Pre-Treatment and Post-Treatment Activities of daily living Evaluation**: *Subjects were asked to circle a number on an activities of daily life (ADL) scale of 0 (normal) to 10 (I need help), correlated to the Wong-Baker Faces scale.*
- **How is your satisfaction with BioWave?** *Subjects were asked to circle a number on a scale of 0 (poor) to 10 (excellent).*

The following questions were included on the survey:

- **BioWave helped me**: *Subjects were asked to check a box indicating if they were experiencing the following: "walk farther, stand longer, sit longer, sleep better, improved mood, and/or lift more," with an additional "Other" line for written responses.*
- **Effect of BioWave on pain medication consumption**: *Subjects were asked to check a box correlated to one of the following: "eliminated, reduced, or stayed the same."*
- **How often do you use BioWave?** *Subject were asked to check a box correlated to one of the following: "multiple times a day, daily, weekly, or monthly."*
- **Approximately how many hours of Pain Relief are you experiencing?** *Subjects were asked to provide a written response.*
- **Has BioWave improved your quality of life?** *Subjects were asked to provide a written response.*
- **Would you like to continue using BioWave?** *Subjects were asked to provide a written response.*

Information was captured using a Salesforce database. No formal hypothesis testing was performed. For survey study, descriptive statistics including number of patients (n), standard deviation (SD), median, minimum maximum, and 95% confidence intervals (CI) are utilized for all continuous variables. For categorical variables, per category, the absolute counts (n), and percentages (%) are created and summarized. Based on survey responses to anatomic region of pain, patients were grouped and mean change in pain and activities of daily living from baseline were compared. Within the survey, patients could write-in the anatomic area(s) where they were experiencing pain. As such, grouping was done in a manner where patients were not duplicatively represented based on variations within the written responses.

Treatment Device

The BioWaveHOME neurostimulator is a non-pharmacologic, non-narcotic, non-addictive, non-invasive treatment for pain **(Figure 1).**

Figure 1: BioWaveHOME Unit

The device works by delivering a back and forth summation of two high frequency sinusoidal alternating current signals at 3,858hz and 3,980hz. Current travels

between two electrodes. Electrodes are placed directly over one or two locations of pain. The mechanism of action that results from the electrical field generated from BioWave devices is similar to chemical anesthetics and is based on Frequency Conduction Block Theory. This technology is in contrast to TENS devices, which are based on Gate Control Theory. The sensation created by the TENS device can create a noxious sensation at the skin surface, acting as a distraction to pain but not blocking the pain signal itself.

The BioWave electrodes through which the high frequency signals are delivered consist either of a B-set or E-Set electrodes (**Figure 2**).

Figure 2: B-Set (Left) and E-Set (Right) Electrodes

B-set: 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).

E-set: 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.

Endpoints

Primary endpoints include changes in pain and function as measured by the NRS Pain Scale and ADL Scale, respectively. Secondary endpoints include quality of life outcomes, including time of pain relief provided, the effect on pain med consumption, satisfaction and desire to continue to use the BioWaveHOME, and if the BioWaveHOME device use improved walking distance, ability to stand or sit for extended periods of time, sleep and mood quality, and ability to lift greater weight. As an exploratory evaluation, improvement in pain and function by anatomic pain location was assessed.

RESULTS

Demographics

Of the 463 subjects with submitted surveys, 374 subjects were male (80.3%) and 91 (19.7%) were women. Mean age was reported as 57 years (Minimum age 37, Maximum age 66). Four-hundred twenty-three subjects were Veterans, 39 subjects were treated at pain or orthopedic clinics.

With regard to type of pain recorded on the survey, 93.3% of subjects responded. Of these responders, 84.9% reported having chronic pain and 19.4% reported having acute pain. Neuropathic pain was reported in 22% of subjects and nociceptive pain was reported in 2.6% of subjects. Subjects could select multiple pain types (e.g. acute, chronic) so overlap exists between these types of pain. In response to how often subjects used the BioWaveHOME device, the majority subjects reported using the device daily (51.0%) or multiple times per day (30.0%).

Effectiveness

As described previously, pain was captured using a 10-point numeric rating scale. Following two weeks of treatment, a significant reduction in pain was reported, with a mean decrease in pain score of 3 points (**Table 1**). The upper bound of the 95% confidence interval is below zero, indicating subjects saw a statistically relevant reduction in pain ($p<0.001$). It can be concluded with 95% confidence that the pain reduction is at least 2.9 for subjects. Plots mapping change in pain are presented in **Figure 3**.

Table 1: Pain Scores

						95% CI	
	Mean	**SD**	**Med**	**Min**	**Max**	**LB**	**UB**
Pre	7.3	1.7	8.0	1.0	10.0	7.2	7.4
Post	4.2	2.0	4.0	0.0	10.0	4.1	4.5
Δ	**-3.0**	**2.0**	**-3.0**	**-10.0**	**6.0**	**-3.2**	**-2.9**

Similarly, a significant improvement in activities of daily living was reported. Note, a reduction in ADL score in the survey indicated an increase in ADL function with the best possible score being 0 ('I feel Great'). Subjects experienced a mean reduction in ADL score of 1.8 points (**Table 2**). The upper bound of the 95% confidence interval is below zero, indicating subjects saw a statistically relevant increase in ADL function ($p<0.001$). It can be concluded with 95% confidence that the ADL function

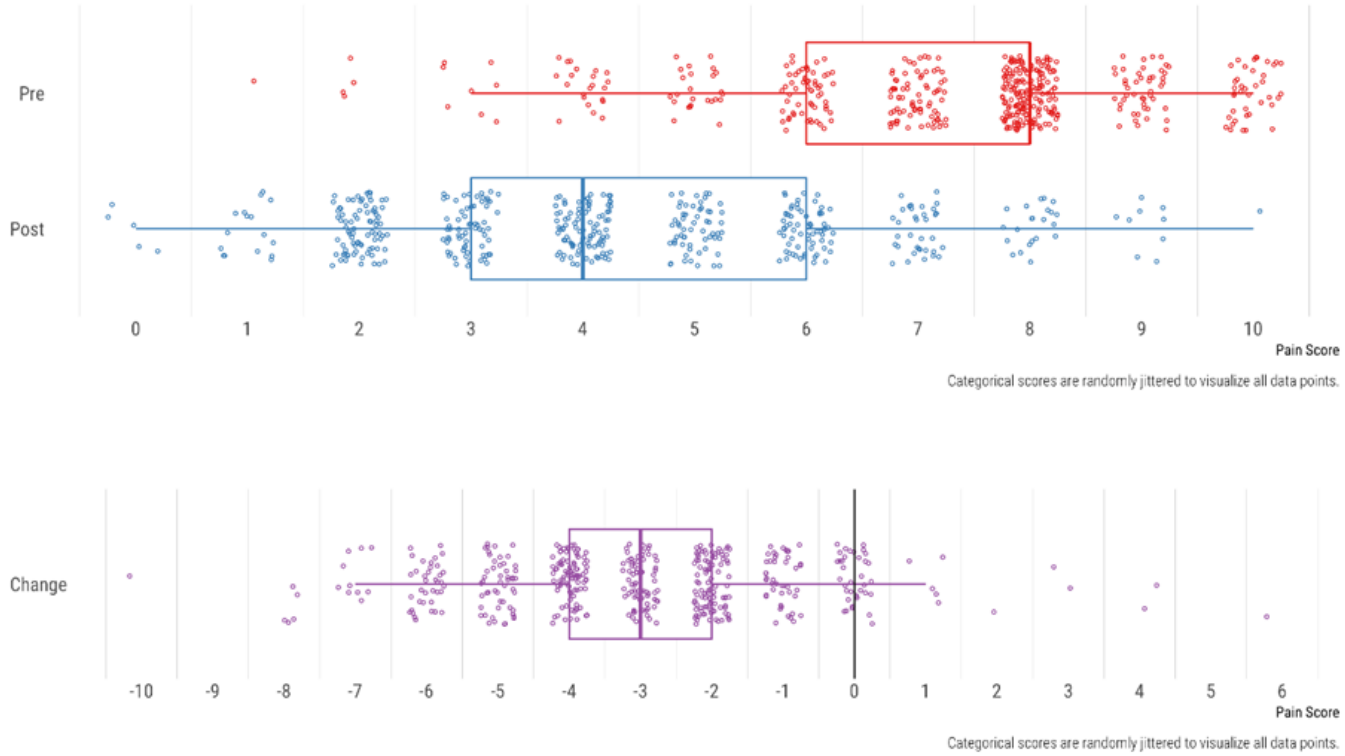

Figure 3: Boxplot indicating Pre- and Post-Treatment Pain Scores (Top) and Change in Pain Scores (Bottom)

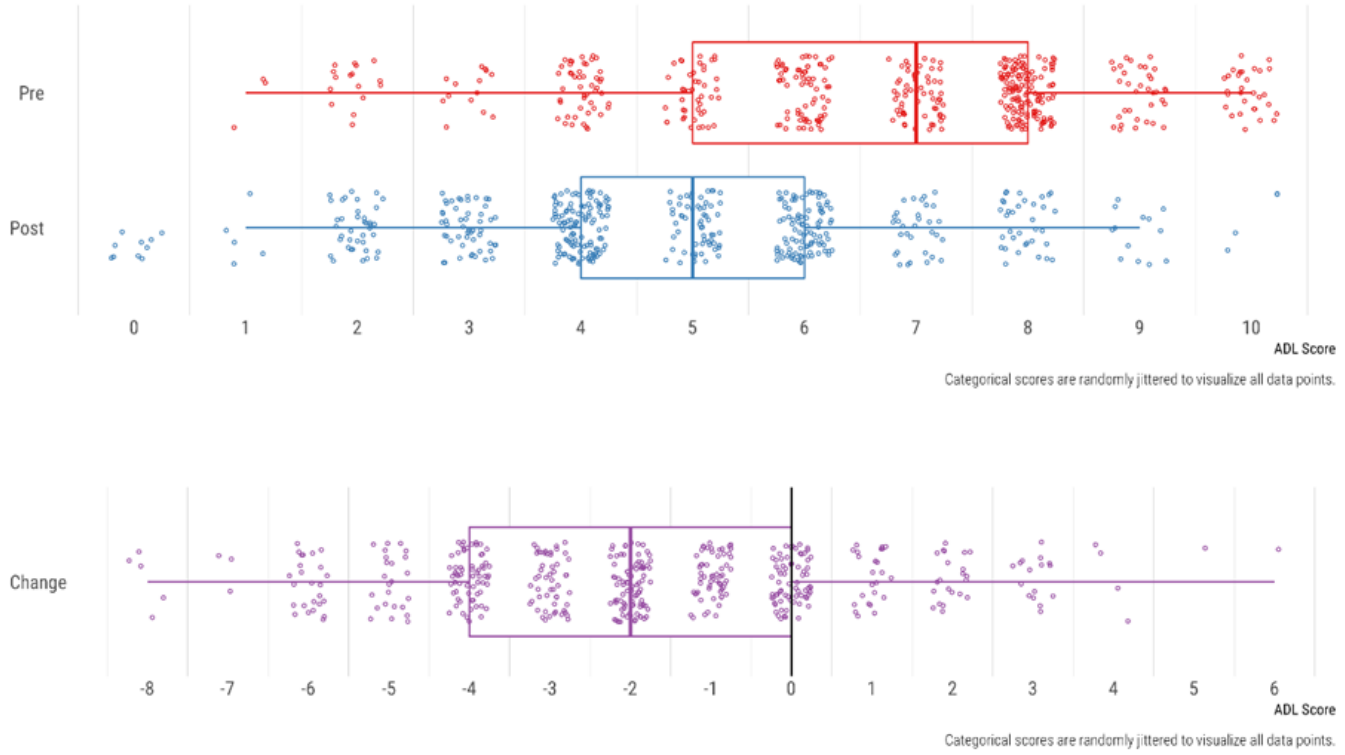

Figure 4: Boxplot indicating Pre- and Post-Treatment ADL Scores (Top) and Change in ADL Scores (Bottom)

increased by at least 1.6 for subjects. Plots mapping change in pain are presented in **Figure 4**.

Table 2: ADL Scores

						95% CI	
	Mean	**SD**	**Med**	**Min**	**Max**	**LB**	**UB**
Pre	6.7	2.0	7.0	1.0	10.0	6.5	6.9
Post	4.8	2.0	5.0	0.0	10.0	4.7	5.0
Δ	**-1.8**	**2.4**	**-2.0**	**-8.0**	**6.0**	**-2.0**	**-1.6**

As demonstrated, two-week treatment with the BioWaveHOME resulted in significant reduction in pain and significant improvement in function as measured by activities of daily living.

As an exploratory analysis, improvement in pain and ADL by anatomic pain location reported on the returned patient survey was evaluated. Grouping patients by area of pain, most patients reported some form of back pain (n=257), with the second most reported area being followed by shoulder pain (n=91). A total of 98 patients did not report a specific region for their pain.

In comparing the different anatomies with regard to change in pain score from baseline, it is clear that no anatomy performed significantly worse than the mean reported improvement (3 points), with most reporting improvements in-line with the overall mean improvement (**Figure 5**). Patients reporting back pain, which encompasses most of the overall patient population, had a mean improvement of ~3 points. Excluding patients that did not report a specific region of pain, the second most reported area of pain was the shoulder (n=91), which reported a mean improvement of ~3.5 points. While numerically higher, this improvement is not significantly different from the overall mean improvement. Similarly, improvement in ADL by anatomy revealed a near identical improvement from baseline for all anatomies, ~1.8 points (**Figure 6**).

When asked how many hours of pain relief was provided by BioWaveHOME, mean time of relief was reported as eight (8) hours, with relief times ranging from 30 minutes to up to 73 hours after each use. With regard to pain medication, over half (51.8%) of subjects reported either reducing or eliminating use of medications for pain during the two-week treatment period.

When asked if BioWaveHOME has improved the subject's quality of life, 87.7% of subjects reported "very much," "yes," or "somewhat." Satisfaction with the BioWaveHOME system was high, with subjects reporting a mean 8.1 points on the 10-point scale used to evaluate treatment satisfaction. Additionally, 97% of subjects reported a desire to continue using the BioWaveHOME system.

With regard to the aspect of life improved by incorporation of the BioWaveHOME system into the subjects' pain management routine, subjects reported being able to walk further, stand longer, sit longer, sleep better, lift more, and be in a better mood during the two-week period where the BioWaveHOME was being used.

Safety

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

DISCUSSION

This study sought to evaluate the effectiveness of the BioWaveHOME system, an in-home, non-pharmacological, non-invasive pain management device. The current study is the second investigation conducted evaluating the effectiveness of the device in subjects with chronic pain. The first study, a survey of 66 Veterans using the BioWaveHOME for long-term use (6-18 months), reported that 90% of subjects described a significant decrease in pain, increased range of motion, or an increased ability to participate in activities of daily life after incorporating the device into an existing pain management routine [8]. Of the study participants, 58.7% reported reducing or eliminating use of prescription opioids while using the BioWaveHOME. While the results from this initial evaluation were encouraging, additional investigations were necessary to evaluate use of the BioWaveHOME in a larger patient population with validated, subject-reported outcome measures. Additionally, the effect of short-term BioWaveHOME use was also important to investigate, as an effective, easy-to-use, in-home alternative to prescription opioids that provides immediate and sustained relief could potentially have a significant impact on how treating physicians view pain management.

This study, inclusive of 463 survey responders, demonstrates that the BioWaveHOME is an effective non-pharmacological, non-invasive, non-addictive pain treatment solution for chronic and acute pain sufferers. Pain, as measured by this evaluation using a numeric rating scale within the provided survey, was found to

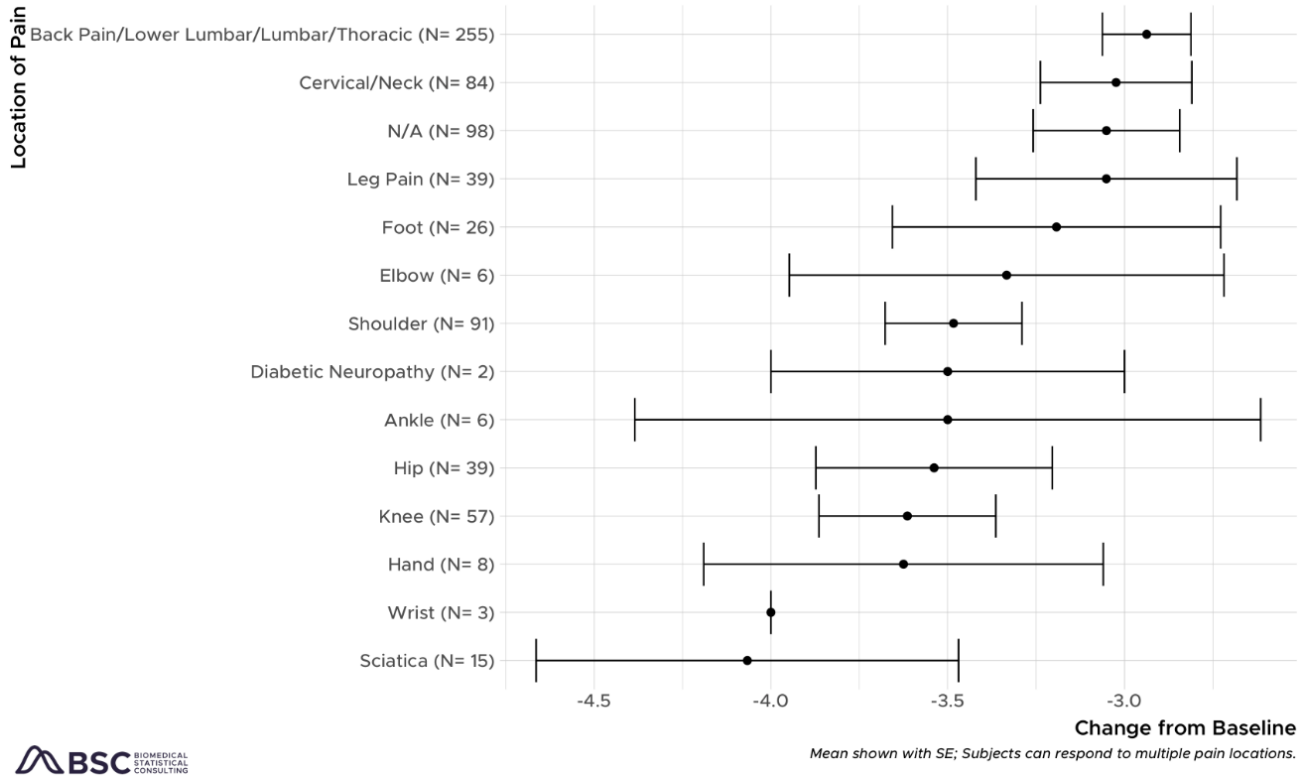

Figure 5: Change in Pain Score from Baseline by Anatomy

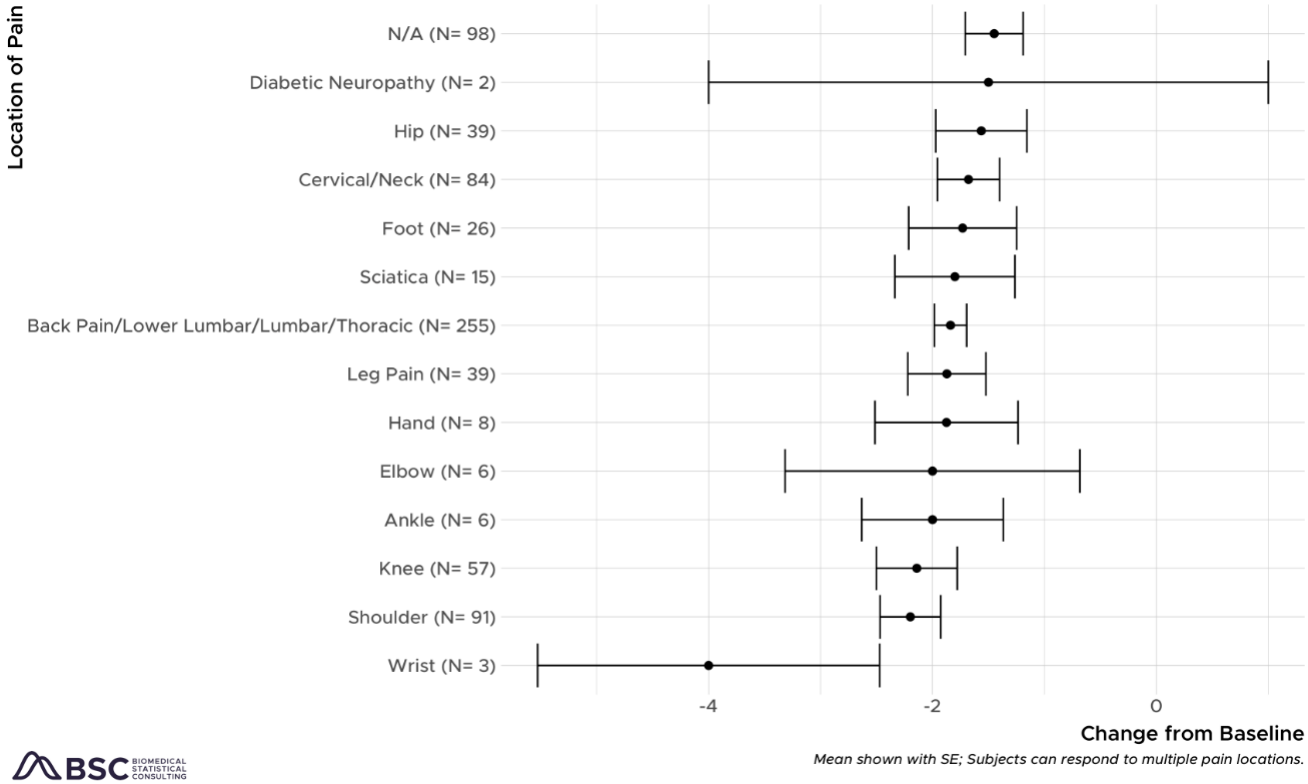

Figure 6: Change in ADL Score from Baseline by Anatomy

significantly decrease following use of the BioWaveHOME. Subjects in the study reported a mean decrease in pain of three (3) points, which is a greater improvement than what is considered to be the minimal clinically important difference (MCID) for general chronic pain (1.7-points) and chronic musculoskeletal pain (1-point) [9]. Within the survey, the pain scale was correlated to the Wong-Baker Faces rating scale, which has been reported to have an MCID of two to three points on a numerical scale [10]. Considering both pain scales, subjects within this study experienced a clinically significant reduction in pain after incorporating the BioWaveHOME device into their pain management routine for two weeks. Importantly, 51.8% reported completely eliminating or reducing pain medication during the two-week treatment period, further supporting the significant relief experienced by subjects when using the BioWaveHOME. Subjects reported an average of eight hours of relief following use of the device, which likely contributed to the subjects being able to reduce pain medication intake or eliminate use completely. Subjects in the study reported a significant improvement in activities of daily living following use of the BioWaveHOME for two-weeks per the patient-reported 10-point scale included within the survey. Pre-treatment, subjects recorded an average of 6.7 points out of 10 on the scale, where increasing numbers correlate to increased disability. Following two-weeks of BioWaveHOME use, subjects reported a mean improvement of 1.8 points, with a post-treatment mean of 4.8 points. Related, the majority of the subjects in the study reported that the BioWaveHOME improved their quality of life, with 87.7% reporting at least some degree of improvement. With these improvements, subjects reported being able to walk farther, stand longer, sit longer, sleep better, and reported having an improved mood while using the BioWaveHOME. Considering both the improvement in pain and reduced disability, the BioWaveHOME was found to considerably improve subject quality of life after just two-weeks of use. Additionally, evaluating pain and ADL improvement by anatomy revealed an important conclusion: significant improvement in pain and function are not exclusive to specific anatomies, all treated areas in the study benefited from treatment with the BiowaveHOME device. While no specific anatomy reported a mean improvement significantly different from the mean pain and ADL improvement, it is encouraging to see the various anatomies reported responding equally to the treatment. One of the most pressing concerns with prescription opioids in chronic pain sufferers is the need to continue medicinal treatment to have continued relief. Long-term opioid use can result in tolerance, which requires more of the drug to create the same level of relief, commonly resulting in opioid misuse, addiction, and, regrettably, overdose. With opioid misuse, users are likely to seek out non-prescription alternatives as these are often less costly and easier to obtain than prescription opioids. A recent survey of active heroin users reported that 80% of users surveyed switch to heroin following opioid misuse [11]. Within this study, over half of the surveyed BioWaveHOME users reported being able to eliminate or reduce pain medication use and reported having an average of eight hours of sustained relief following each use of the device. As a non-opioid, non-addictive simple-to-use treatment device that can be used in-home, this study supports that the BioWaveHOME system could provide a viable alternative to prescription pain medication that is effective and sustained.

Non-opioid alternatives to pain management are not novel. TENs units are non-pharmacologic, non-addictive, non-invasive devices that can be incorporated into existing pain management routines. The main limitation of the TENs technology is that it is based on the "gate control theory" of pain, which focuses primarily on masking pain signals. By masking pain signals, relief is only short-term. The technology behind the BioWaveHOME, alternatively, 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. Through this pathway, the action potential does not move through the pain fibers, stopping the pain signal. The BioWave technology is able to provide long-term relief by blocking the pain signal, as evidenced by the long periods of relief reported by the subjects within this study.

Considering the increasing public health burden and healthcare costs of the opioid epidemic in both the general and Veteran populations and the current lack of effective commercially available alternatives, this study demonstrates that the BioWaveHOME has the potential to meet an unmet healthcare need: an easy-to-use, non-addictive alternative to pain management that has been shown to be effective in providing immediate pain reduction and improving quality of life. Almost all of the surveyed subjects reported wanting to continue using the device, with 73.2% of subjects reporting a

satisfaction of 8, 9, or 10 on a 10-point scale of increasing treatment satisfaction. Overall, the BioWaveHOME was effective at significantly reducing pain and improving function in the surveyed group and provides a viable alternative to prescription drug pain management.

CONCLUSIONS

In conclusion, the BioWaveHOME was found to effectively and significantly reduce pain and improve quality of life following two-weeks of as-needed use. In addition, the majority of study subjects reported great satisfaction with the treatment, with most reporting reducing or eliminating prescription pain medication use and expressing a desire to continue using the device.

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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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October 2017

Musculoskeletal Clinical
Regulatory Advisers, LLC

MCRA Whitepaper

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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).

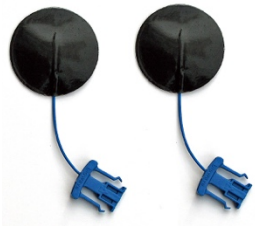

Figure 2: B-Set Electrodes

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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BioWave White Paper on Use of a Neuromodulation Pain Therapy Device (“BioWavePRO®”) to Treat Acute Sports Injuries

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Joseph Pergolizzi, M.D.

Introduction:

A high percentage of both acute and chronic sports related pain is associated with back or extremity injuries. It is estimated that greater than 70% of all sport injury related pain is treated with traditional analgesic medications in an outpatient setting. Although there is a considerable documentation of the incidence and severity of both acute and chronic pain using these traditional methods in the general population, there is very little data regarding the utilization of non-invasive medical devices. Because professional athletes depend on their physical abilities to generate financial income and achieve professional advancement, it is imperative that their pain be addressed in an optimal manner. 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. This is especially relevant to professional athletes who rely on both physical and mental abilities to be able to remain competitive in their profession. Moreover, many of these athletes are subject to various substances testing in order to maintain eligibility to practice in the sport, and therefore it is assumed they would rather bear the pain and avoid treatment than potentially be prohibited to play. This can lead to under-reporting and under-treatment of pain in this particular setting. Thus there is an unmet need for therapies that may lessen the pain related to sports injuries and the side effects related to traditional treatment modalities.

Biowave Corporation's BiowavePRO® Neuromodulation Pain Therapy Device ("BiowavePRO" or the "Device") utilizing Biowave Noninvasive Reusable Electrodes has been studied in an open label manner in regard to efficacy and tolerability in the treatment of pain associated with injury in a professional sports environment. The BiowavePRO device has been tested on injuries affecting the players of the NY Giants professional football team.

Methods:

Inclusion criteria:

1. Patients must be male of any race
2. American Society of Anesthesia Physical Classification: ASA 1-3 [American Society of Anesthesiologists (ASA): New Classification of physical status. Anesthesiology 24:111, 1963]
3. Ages 18- 40 yr
4. Patients must have a baseline score of ≥30 mm on the VAS pain scale
5. If taking analgesics, patients must agree to maintain a steady regimen for the duration of the study
6. Patients must be able to understand and be willing to cooperate with study procedures
7. Able to provide written and verbal informed consent

Any football player in training camp and active and practice squad members during the playing season who were injured were eligible to participate. Treatment would be offered on a daily basis until the condition resolved, or until the subject was no longer able to participate (i.e. dismissal as a member of the team).

Exclusion Criteria:

1. Allergy or intolerance to adhesive materials
2. Surgical intervention during the past month for the treatment of the painful site or its underlying etiology
3. Clinical evidence of cardiovascular (history of cardiac arrhythmias), pulmonary, renal, psychological, hepatic, neurological (seizures), hematologic, or endocrine abnormalities
4. History of any substance abuse or dependence within the last 6 months
5. Patients with pending Worker's Compensation claims, pending civil litigation pertinent to the cause of pain, currently receiving monetary compensation for the injury resulting in pain, or currently involved in out-of-court settlements for claims pertinent to their pain
6. History of pacemaker, implantable devices (AICD, pump, etc.)
7. Patients who have received an investigational drug or device in the past 30 days.

Treatment Algorithm:

If all of the inclusion criteria were met and none of the exclusion criteria were met, the informed consent form was reviewed with the patient for signature. The patient was then enrolled into the study treatment group. The patient's demographics (date of birth, race), brief medical history, vital signs (blood pressure, heart rate, temperature, and respiratory rate), focused physical examination (including range of motion [ROM]), and concomitant medications were noted on the CRFs. As part of the brief medical history, the patient indicated the date and site of injury, and marked the area of perceived pain on a front and rear view human figure. A member of the study team instructed the patient on how to use

a Visual Analog Scale (VAS), where "0" is none and "100" is worst pain possible. The patient then indicated the intensity of pain with a visual analog scale (VAS) score.

Prior to the treatment session, the patient completed the initial pain evaluation (VAS). The patient's range of motion (ROM) was assessed. To measure ROM, a goniometer was used to measure the angle of the range of motion. For back pain, the patient was asked to bend forward at the waist, bend to the right and to the left at the waist and to arch their back. For joint pain, the patient was asked to extend the joint to its greatest range of motion (extension), and then flex the joint as far as possible (flexion). ROM measurements were made accordingly. Treatment was initiated with the device after adequate placement of the electroconductive pads. The investigator controlled the amplitude of the signals. Patients would ask the investigator to increase the signal strength until a strong but comfortable sensation was obtained, from which point treatment will continue for twenty (20) minutes. Patients may ask the investigator to increase or decrease the strength of the signal at any time during the treatment.

Treatment with the BiowavePRO device was administered with a mixed feed frequency signal equal to 3.878 kHz + 4.000 kHz. The investigator recorded Voltage and Percent of Maximum Power achieved from the LCD display before turning off the device.

The electrode pads consisted of a large Feed Electrode placed opposite the pain site and a smaller Pain Site Electrode, placed directly over the source of pain. These pads were placed initially as per the manufacturer's directions, but were adjusted based on the feedback from the study subjects. For joint pain, the initial electrode configuration consisted of placing a 1.25" diameter Pain Site Pad over the site of pain complaint, with a 2.25" x 4" Feed Pad positioned 180 degrees in opposition to the first pad, or in as much of an opposing manner as possible. For subjects with low back pain or hip pain, a 2" diameter Pain Site Pad was placed over the site of pain, with a 5" x 8" Feed Pad placed over the abdomen or quadriceps, respectively. Treatment was performed with continued increase in power output to the maximally tolerated level, and then maintenance at that level for a 20 minute session. BiowavePRO was utilized as part of a first-line treatment algorithm in conjunction with anti-inflammatories and ice. The majority of the subjects received ice during the treatment session, which is the facility standard of care when utilizing any electro-therapy equipment.

The subjects received the initial treatment, which was initiated between 6:30 am and 7:00 am, prior to the practice session. Pain assessments took place immediately post-treatment, 4 hours post-treatment, after practice session (10-12 hours post-treatment), and 24 hours post-treatment (next morning). Some of the subjects received a second treatment after the conclusion of the practice session, especially those who had suffered a new acute injury during that practice session. The subjects were allowed to perform exercise or receive rehabilitation treatments while undergoing treatment with the BiowavePRO device. Examples of this concurrent activity includes the use of upright and recumbent exercise bikes, use of elliptical machines, VersaClimber, and active leg extensions up to 40 degrees.

After the device was turned off and the electrodes removed, VAS pain evaluations, ROM tests, and patient global impression of change were obtained at 0, 6 and 24 hours following discontinuation of therapy. ROM test were not performed at 6 and 24 hours. Assessments of tolerability and acceptability were performed at the 0 hour interval. Questions were focused to the acceptability of the treatment procedure and overall satisfaction with treatment.

Results:

Over a two-year period, approximately 160 players were available to participate in the study. Ninety players participated in training camp, 53 active players and 7 practice squad members during the season, and 25 players on injured reserve. Eighty individuals had received at least one BiowavePRO treatment, approximately 50% of the eligible population. The treatment subjects were enrolled with a diagnosis that included one of the following: foot sprain, ankle sprain, knee sprain, tendonitis of the knee, hamstring injury, cervical discogenic pain, lumbar discogenic pain, anterior cruciate ligament contusion, osteoarthritis of the knee, labral tears of the hip, quadriceps contusion, shoulder injury, and cervical pain/ neck injuries. Achille's tendonitis, patella femoral, calcaneal fasciitis, plantar fasciitis, and OCD knee defect were also included.

A total of 600 treatments were provided to the study participants. The majority of participants, 66%, received treatment for 7 to 10 days. 17% of participants received treatment up to one month, 12% received treatment up to three months, and 5% received treatment for as long as 6 months. The patients who required treatment for 6 months did not report a decline in efficacy over time. These individuals had diagnoses including low back pain, post ACL repair, leg fracture, patella tendonitis, and Achilles tendonitis. Shoulder injury patients represented the majority of individuals who received treatment for up to 3 months.

Efficacy:

Less than 5% of the participants reported no benefit from the treatment. The majority of subjects reported significant relief immediately following treatment, with maintenance of the benefit for 4 to 6 hours. The majority of players either aggravated the existing injury or incurred a new injury, which necessitated a repeat treatment after the practice session was concluded for the day. This significantly reduced the number of participants who would be able to give a 12 hour and 24 hour post-treatment assessment.

In regard to patient global impression, the majority of subjects would request the BiowavePRO treatment with a perceived superiority in comparison to other electro-therapy devices they had used. None reported a decline in treatment effect with repeated use, even the patients who had utilized BiowavePRO for a 6 month duration.

In regard to clinician global impression, the team trainer rated BiowavePRO as "much more effective than TENS or the RICHMAR Interferential device". The team physician also was impressed by BiowavePRO as a superior treatment, adding that it enabled the

participants who had tendonitis or tendonosis to continue training, which is unusual with currently available therapy.

Adverse Events:

There were no reports of any burns, or any electro-thermal injury. A small number of players reported a "shock-like" sensation, but did not feel that this was different from the sensations perceived when using other electric stimulation devices.

Conclusions:

This is the first study of the use of the BiowavePRO device to treat the pain associated with sports-related injuries. The device was found to be well tolerated by the majority of study subjects. The subjects expressed great satisfaction with the treatments, and requested repeat treatments. The clinicians global impression was very favorable, which led to a request and use of the device for the U.S. Olympic swim team prior to and during the 2004 Olympics, as well as continued use of BiowavePRO for a third year with the NY Giants. This device, with very little downside from a risk perspective, is well suited to be used as a first line treatment for the treatment of pain from sports related injuries. Future studies to be performed in professional basketball and baseball players will give needed additional information in regard to the applicability of our results to athletes in general.

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

JUNE 2007 | Volume 30 • Number 6

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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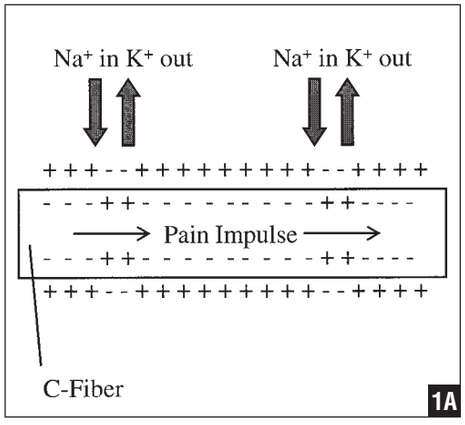

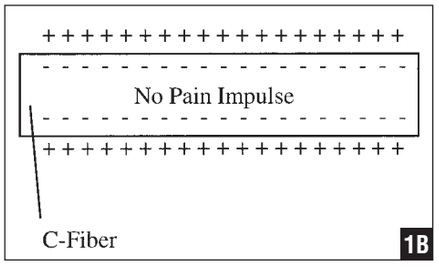

Figure 1: Deepwave (Biowave Corporation, Norwalk, Conn) mechanism of action via frequency conduction block. Normal propagation of pain signal along pain fibers (C-fibers) (A). Deepwave electric field interrupts sodium/potassium ion exchange, thereby inhibiting the cell wall from changing polarity and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

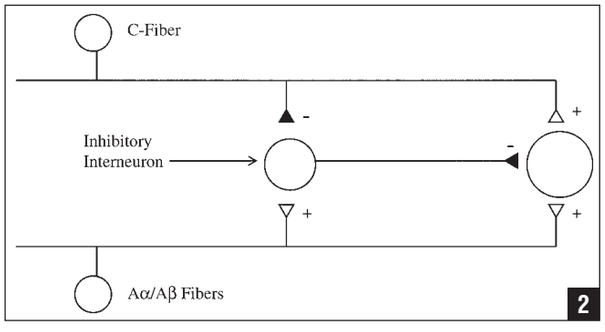

Figure 2: Deepwave (Biowave Corporation, Norwalk, Conn) mechanism of action via the gate control theory. The Deepwave may also activate the Aα/Aβ fiber, which occurs at both the inhibitory interneuron and projection fiber, thus causing a suppression of the pain sensation.

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.

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

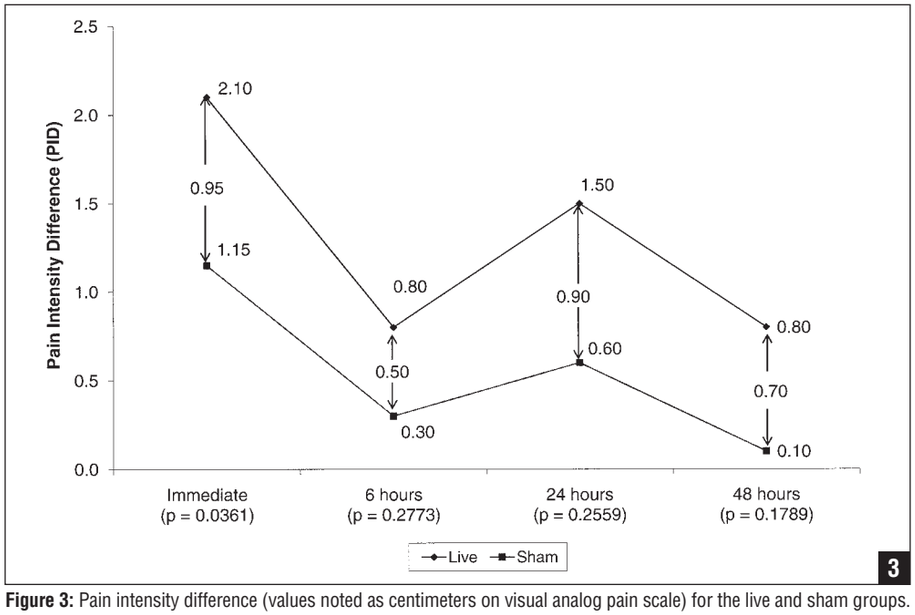

Figure 3: Pain intensity difference (values noted as centimeters on visual analog pain scale) for the live and sham groups.

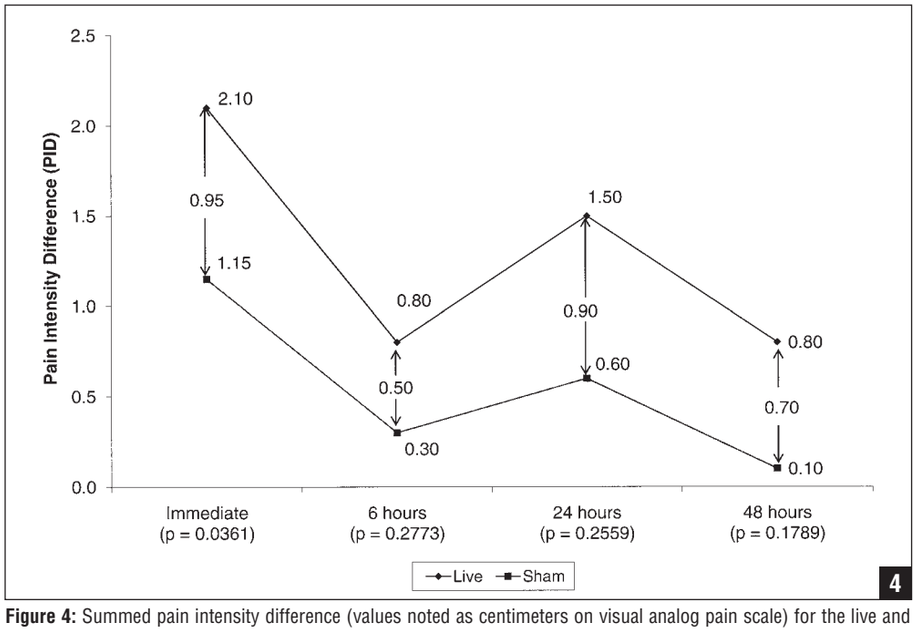

Figure 4: Summed pain intensity difference (values noted as centimeters on visual analog pain scale) for the live and sham groups.

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

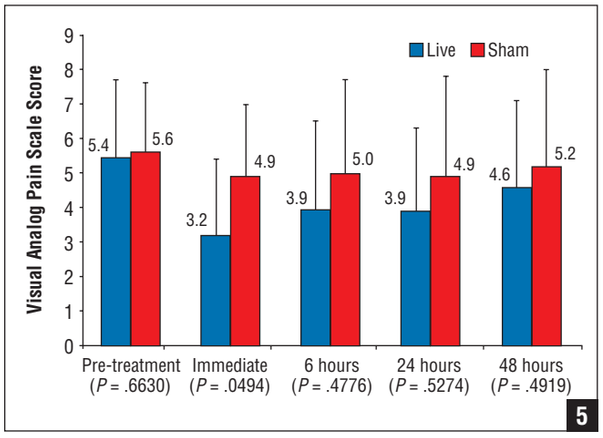

Figure 5: Raw visual analog pain scale scores recorded for live and sham groups. Significance is noted at the immediate post-treatment period.

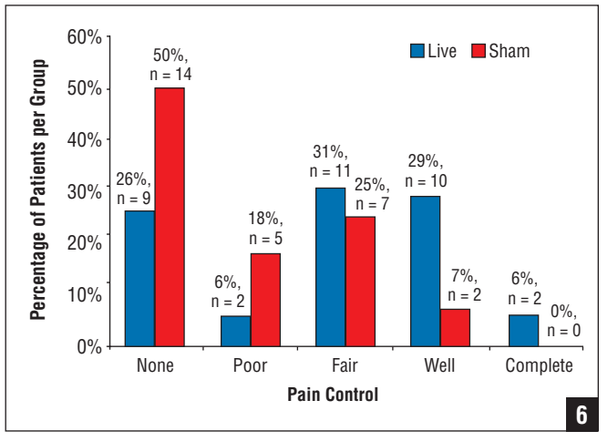

Figure 6: Distribution of pain control assessed at 48 hours post-treatment. The live group has significantly better pain control than the sham group (P=.039).

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

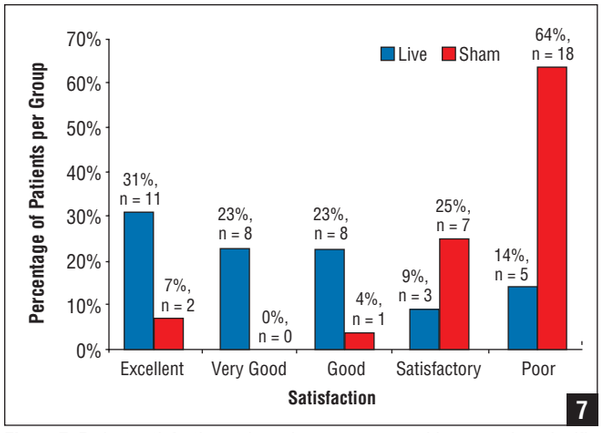

Figure 7: Patient satisfaction at 1-week post-treatment. Live group has significantly higher patient satisfaction than the sham group ($P<.0001$).

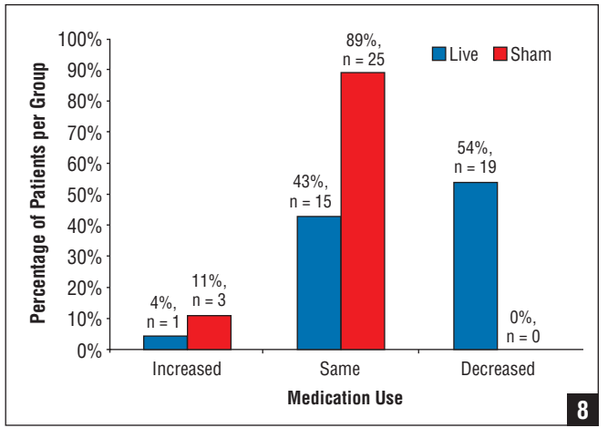

Figure 8: Medication use reported at the 1-week post-treatment. The live group had significantly less medication use ($P<.0001$) than the sham group.

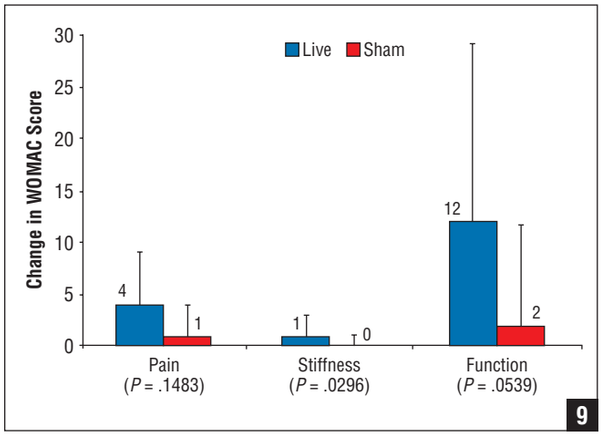

Figure 9: Change in WOMAC score from pretreatment to 48 hours post-treatment. The live group was statistically significantly different from the sham group for the stiffness assessment.

($P<.0001$) 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 posttreatment. 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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Section Editor: Bennie G.P. Lindeque, MD

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.

LocHospital 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, Henderson, Nevada

Poster Presentation: American Academy of Orthopaedic Surgeons 2009 Annual Meeting, February 25-28, 2009, Las Vegas, Nevada

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**

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 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

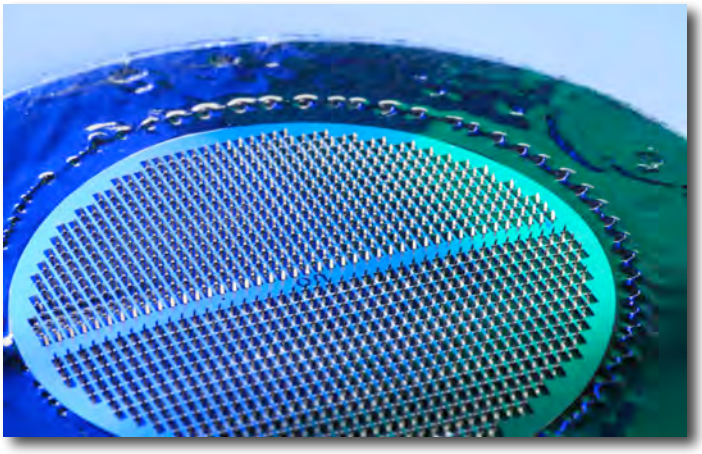

Figure 2

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.

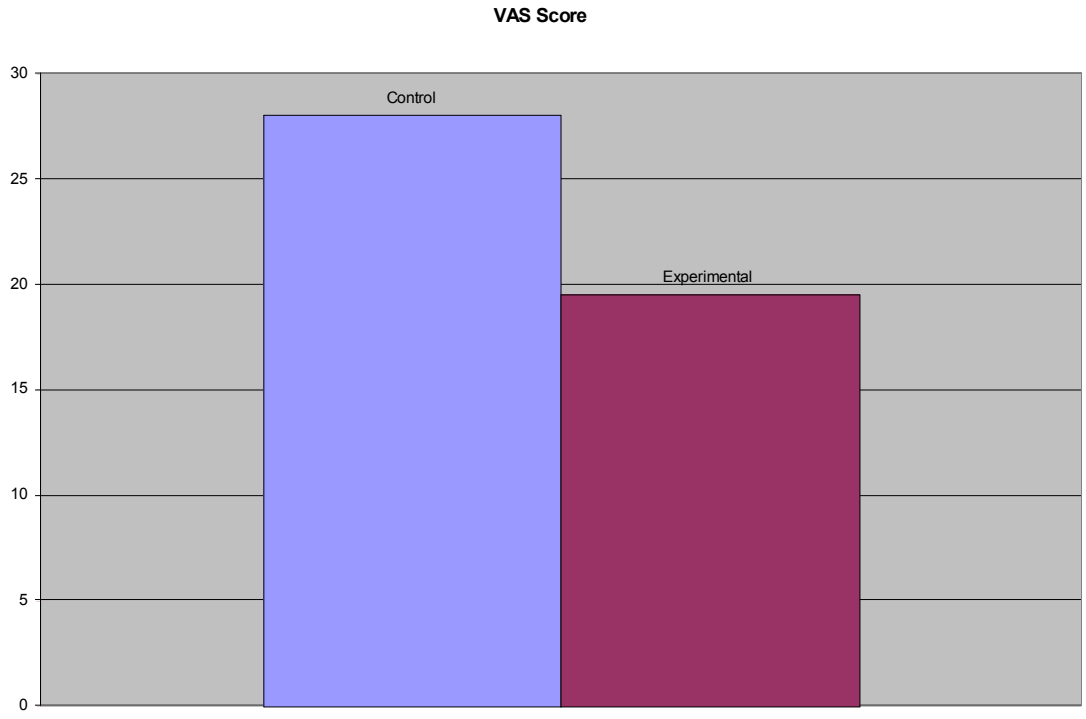

Figure 3: VAS Score

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 ($p = .09$).

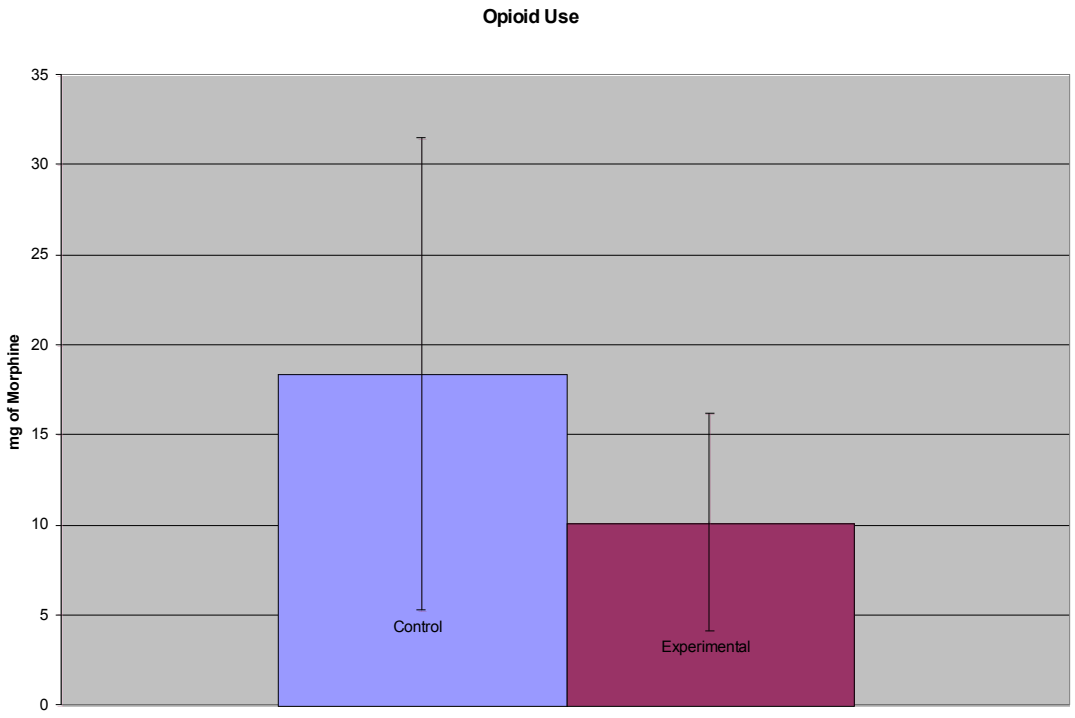

Figure 4: Opioid Use

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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Summary of a Randomized, Double-Blinded, Comparative Crossover Trial of the Safety and Efficacy of a Non-Invasive Targeted Electronic Pain Control Device (“BioWave System”) Versus Transcutaneous Electrical Nerve Stimulation (TENS) for the Symptomatic Treatment of Chronic Low Back Pain; March 2006

Weill Medical College of Cornell University
New York Presbyterian Hospital
New York, NY

Principal Investigators: S. Panchal MD, H. Hemmings MD, PhD, S. Diwan MD

Summary of a Randomized, Double-Blinded, Comparative Crossover Trial of the Safety and Efficacy of a Non-Invasive Targeted Electronic Pain Control Device ("Biowave System") *Versus* Transcutaneous Electrical Nerve Stimulation (TENS) for the Symptomatic Treatment of Chronic Low Back Pain; March 2006

Location: **Weill Medical College of Cornell University**
New York Presbyterian Hospital
New York, NY

Principal Investigators: S. Panchal MD, H. Hemmings MD, PhD, S. Diwan MD

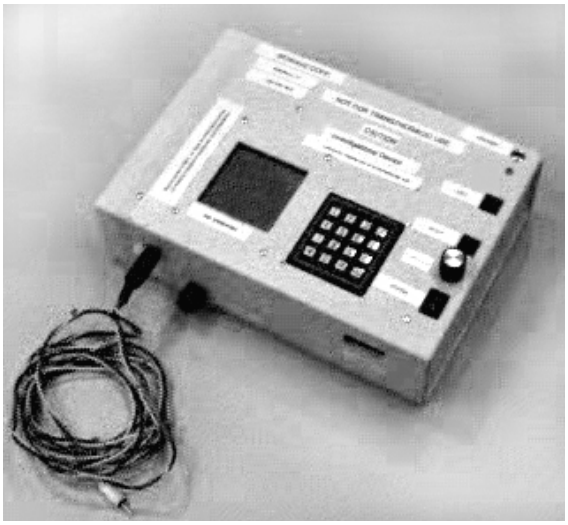
1. Introduction

Low back pain is a common, costly and often chronic condition, estimated to affect up to 85% of people in their lifetime. The direct medical costs and indirect costs, including disability and lost wages, of low back disorders are estimated at $50 - $100 billion per year. Current treatments are less than ideal: commonly used opioid and non-opioid analgesic drugs produce adverse effects, while many non-pharmacologic therapies are invasive or of questionable therapeutic value. New therapies for the effective management of chronic back pain are clearly needed.

The Biowave System (Biowave Corporation, Norwalk, CT) introduces two summed alternating current high frequency sine waves into the body through a first disposable non-invasive round electrode (2 inches in diameter) placed on the skin directly over the pain site. Polarized structures inside the body including nociceptive pain fibers cause the two summed high frequency signals to multiply together forming a new spectrum of signals in a 3-inch diameter hemisphere beneath the first electrode. The multiplication of the two sine waves is known as a Fourier Transform. One of the signals formed resulting from the multiplication is a low frequency signal in the form of an active electrical field that is optimized for hyperpolarizing C-fibers and inducing hypoesthesia on A-delta fibers that fall within the 3-inch diameter hemisphere inside the body. Because the device is an alternating current device, instantaneously the device alternates the delivery of the summed high frequency signals to the second electrode. The active electrical field forms in a hemisphere beneath the second electrode. The device alternates the delivery of the summed high frequency signals back and forth so quickly between the two electrodes, that the patient cannot distinguish that the signals have left either location. The net effect is there are two active electrodes, each of which can treat a distinct volume of tissue simultaneously and there is no noxious twitching sensation.

The use of different sized electrodes concentrates the electric field in the volume of tissue surrounding and beneath the smaller round electrode which must be placed over the location of pain. The sensation felt by the patient is a comfortable pressure and tingling sensation without muscle twitching or the noxious sensation that is common with other electrotherapy devices. This Biowave technology is being explored as a novel therapy for treating chronic, acute or post-surgical pain in the low back, shoulder, neck, hip, knee, elbow, face, legs, arms, wrist, hands, ankles and feet.

2. Biowave Device



The prototype device measures 7.87 inches wide, 11 inches long, and 3 inches deep, weighs about 3.75 pounds, and operates on two 6-volt rechargeable batteries which are enclosed within the unit. The unit will not operate while it is plugged into the wall to recharge the batteries. The patient controls the amplitude of the signal with two buttons (an UP arrow, and a DOWN arrow) on a keypad on the face of the device. An LCD displays the amplitude of the signal in a bar graph and numerical format. Two wires emanate from the unit. One wire is attached to a large dispersive electrode ("Feed Electrode") placed opposite the pain site. The second wire is attached to a smaller round electrode ("Pain Site Electrode") placed over the location of pain (the treatment site).

3. Methods

The IRB approved study was a double blinded, randomized, controlled crossover trial for the treatment of chronic low back pain. The study was conducted at Weill Medical College of Cornell University/New York Presbyterian Hospital in New York City. The purpose of the study was to show that (1) the Biowave System has superior efficacy over an active control, specifically a TENS (Transcutaneous Electrical Nerve Stimulation) device for the treatment of chronic low back pain, and (2) that the Biowave System provides a much longer residual period of pain relief than TENS following a 20-minute duration treatment.

In order to be eligible for the study, patients had to record a baseline pain measurement of 40 mm or higher on a visual analog scale (VAS) that was 100 mm in length. Once a patient was enrolled in the study, they were exposed to both devices through the use of a crossover design. The order of the devices to which each patient was exposed, was randomly determined before the study began. The advantage of a crossover design is that the comparison of Biowave vs TENS is conducted on the same patient, for all patients participating in the study, which provides greater statistical significance for a given treatment group size.

36 treatments were performed on 18 patients. Each patient received one treatment on each device. The treatments were separated by one week to ensure a proper washout period between the two devices. The patients were blinded from the devices by having the devices concealed within a large carton. There were two investigators: the investigator interviewing the patient and collecting initial patient data was also blinded from which device was being used; the second investigator was responsible for controlling the intensity of the device. For each treatment, the leadwires and electrodes were identical in appearance: 3 leadwires emanated from the carton and 3 electrodes were placed on the patient. One large 8" x 5" dispersive electrode was placed on the abdomen, and two smaller 2-inch diameter round electrodes were placed on the lower back directly over locations of pain. For the Biowave treatment, only one of the small round electrodes on the lower back and the dispersive electrode on the abdomen were active and the active smaller round electrode was placed directly over the location of pain in the lumbar area including over the lumbar spine. For the TENS device, only the two round electrodes on the lower back were active and the two electrodes were placed bilaterally surrounding the pain site.

Before being exposed to each device, the patient recorded the level of both their surface back pain and their deep back pain on the visual analog scale (VAS). The patient's range of motion (ROM) was also assessed at baseline according to the protocol description. Each patient was then exposed to the first device for 20 minutes. Subsequently, the patient recorded their level of surface pain and deep pain at 0, 30, and 60 minutes

following treatment, and in addition, at 4, 6, 12 and 24 hours following treatment. The patient's ROM was also re-assessed at 0, 30, and 60 minutes following treatment. A period of at least one week was allowed to pass before each patient was exposed to the second device.

4. Results

The data shows that the Biowave System is safe, provides significantly better and longer lasting pain relief than TENS, and that the Biowave System provides pain relief for up to 24 hours for patients suffering from chronic low back pain.

Nine patients were exposed to TENS first and Biowave second, while nine patients were exposed to Biowave first and TENS second.

There were no adverse events amongst any patients in both of the treatment groups.

Below are tables and charts with data from the study summarizing the results for the 18 patients. Patients completed two sets of Pain Visual Analog Scale (Pain VAS) scores for baseline and post treatment pain scores. One set is for evaluating "Deep Pain" and one set is for "Surface Pain". The tables and charts show data for average percent reduction in VAS pain scores at different points in time from baseline (pre-treatment) to 24 hours post treatment for both Deep and Surface pain.

The data shows not only that the Biowave System is more efficacious, but also that it has a substantially longer residual carryover effect when compared against TENS. This is true for the analyses shown in the charts for both Deep Pain and Surface Pain.

4.1 Deep Pain

The results in Table 1 and Figure 1 show that the average percent reduction in VAS pain scores for deep pain for the Biowave System across all 18 patients was a 75.3% reduction in pain at 1 hour post treatment and 53.4% reduction in pain at 24 hours post treatment, versus 62.7% at 1 hour and 36.8% at 24 hours for TENS.

Table 1

DEEP PAIN AVG % REDUCTION in VAS (n=18 patients)			
Time (Hrs)	Biowave	TENS	Biowave Improvement over TENS
0	61.9%	65.7%	-6.2%
0.5	68.8%	56.6%	17.7%
1	75.3%	62.7%	16.8%
4	69.4%	61.4%	11.6%
6	66.8%	58.0%	13.2%
12	56.5%	50.5%	10.6%
24	53.4%	36.8%	31.1%

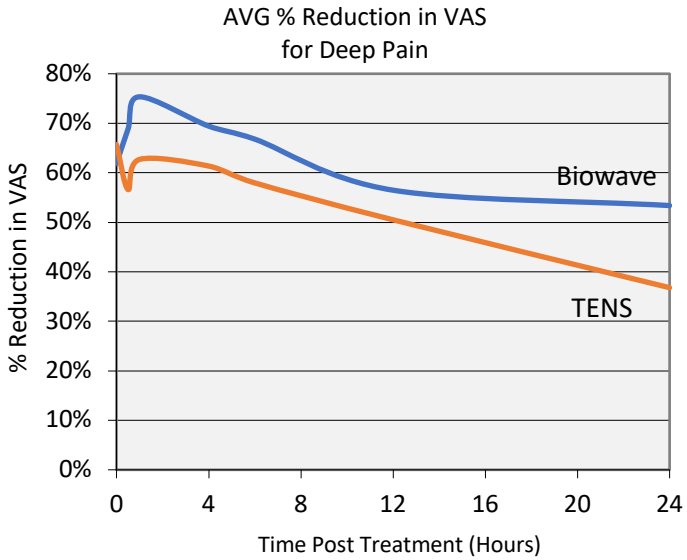


Figure 1. Average Percent Reduction in VAS for Surface Pain- Cornell Double Blinded Controlled Randomized Crossover Chronic Low Back Pain Study

4.2 Surface Pain

The results in Table 2 and Figure 2 show that the average percent reduction in VAS pain scores for surface pain for the Biowave System across all 18 patients was an 82.4% reduction in pain at 1 hour post treatment, 81.8% reduction in pain at 6 hours post treatment and 73.2% reduction in pain at 24 hours post treatment, versus 62.9% at 1 hour, 62.8% at 6 hours and 36.1% at 24 hours for TENS.

Table 2

SURFACE PAIN AVG % REDUCTION in VAS (n=18 patients)			
Time (Hrs)	Biowave	TENS	Biowave Improvement over TENS
0	73.9%	68.0%	8.1%
0.5	81.7%	62.0%	24.2%
1	82.4%	62.9%	23.7%
4	82.8%	65.5%	20.9%
6	81.8%	62.8%	23.1%
12	77.0%	57.8%	24.9%
24	73.2%	36.1%	50.7%

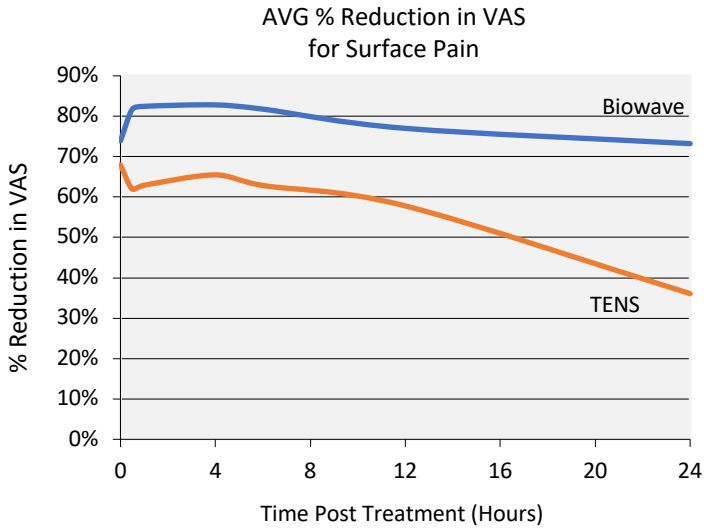


Figure 2. Average Percent Reduction in VAS for Deep Pain Cornell Double Blinded Controlled Randomized Crossover Chronic Low Back Pain Study

The controlled, crossover, randomized, double blinded results show that for the treatment of chronic low back pain, the Biowave System has as much as a 23.7% improvement over TENS at one hour post treatment, and as much as a 50.7% improvement in magnitude of pain relief over TENS at 24 hours post treatment.

4.3 Deep Pain vs Surface Pain

The results of the study show that within each treatment arm there is a small difference in the average percentage reduction in VAS pain scores between the evaluation of Deep Pain vs Surface Pain for the same device at the same time interval post treatment. It was noted during the study that the majority of patients had a very difficult time differentiating between "Deep Pain" and "Surface Pain." As a result, a second analysis was performed by averaging each patients' Deep Pain and Surface Pain VAS scores at each time interval.

Table 3

AVG % REDUCTION in VAS (n=18 patients/36 treatments)			
Time (Hrs)	Biowave	TENS	Biowave Improvement over TENS
0	63.6%	70.4%	-10.7%
0.5	67.6%	64.4%	4.6%
1	69.6%	67.0%	3.8%
4	74.1%	62.8%	15.2%
6	72.6%	59.6%	17.9%
12	65.7%	51.5%	21.6%
24	62.6%	35.0%	44.2%

In this analysis shown in Table 3 we analyze the average Deep and Surface Pain VAS scores for each patient for both Biowave and TENS treatments at each time interval post treatment. The average percent reduction in VAS pain scores for the Biowave System across all 18 patients was an 69.6% reduction in pain at 1 hour post treatment, 74.1% reduction in pain at 4 hours post treatment and 62.6% reduction in pain at 24 hours post treatment, versus 64.4% at 1 hour, 62.8% at 4 hours and 35.0% at 24 hours for TENS.

Biowave treatments provide increasing pain relief over the first 4 hours as compared to TENS where pain relief drops immediately post treatment and at 24 hours post treatment Biowave has a 44.2% improvement in magnitude of pain relief over TENS.

4,4 Duration of Pain Relief Post Treatment

The duration of pain relief 24 hours post treatment for both Deep Pain and Surface Pain was significantly better for patients when treated with the Biowave System then when treated with TENS.

4.4.1 Deep Pain

As shown in Figure 1, for Deep Pain, in the Biowave treatment arm, patients' pain relief *improved* over the first 1 to 2 hours post treatment, as compared to the TENS arm, where the level of patients' pain relief exhibited an immediate decline post-treatment. The magnitude of pain relief was better for patients treated in the Biowave treatment arm as compared to the TENS treatment arm for each time period measured starting at 30 minutes post treatment to 24 hours post treatment.

At 24 hours post treatment the Biowave System had a 31.1% improvement in magnitude of pain relief over TENS.

4.4.2 Surface Pain

As shown in Figure 2, for Surface Pain, in the Biowave treatment arm, patients' pain relief *improved* over the first 4 hours post treatment, as compared to TENS, where the level of patients' pain relief exhibited an immediate decline post-treatment. The magnitude of pain relief was better for patients treated with Biowave as compared to TENS at each time measured from immediately post treatment to 24 hours post treatment.

At 24 hours post treatment the Biowave System had a 50.7% improvement in magnitude of pain relief over TENS.

4.5 Percentage of Patients that Experienced Significant Pain Relief

Results show that more than 80% of patients receive significant pain relief over a 24 hour period post treatment.

Reduction in VAS Pain Scores of at least 30% is generally considered by pain health care providers to be a significant reduction in pain which more than accounts for potential placebo effects.

As shown in Table 4, when patients received a Biowave treatment, at 1 hour post treatment 88.5% of patients received greater than a 30% reduction in their VAS Pain Score. At 24 hours post treatment, as many as 80% of patients were still experiencing greater than a 30% reduction in their VAS pain score.

Reduction in VAS Pain Scores of at least 50% is considered even more significant for any type of pain treatment modality.

As shown in Table 5, When patients received a Biowave treatment, at 4 hours post treatment, as many as 85.0% of patients received greater than a 50% reduction in their VAS Pain Score. At 24 hours post treatment, as many as 70% of patients were still experiencing greater than a 50% reduction in their VAS pain score.

The results show that Biowave provides significant chronic pain relief for as many as 80% of patients treated at 24 hours post treatment.

Table 4

Percentage of Patients with >30% Reduction in VAS Pain Scores		
Time (Hrs)	**Deep pain**	**Surface Pain**
0	76.9%	80.8%
0.5	80.8%	80.8%
1	88.5%	88.5%
4	85.7%	95.0%
6	80.0%	90.0%
12	80.0%	85.0%
24	75.0%	80.0%

Table 5

Percentage of Patients with >50% Reduction in VAS Pain Scores		
Time (Hrs)	**Deep pain**	**Surface Pain**
0	69.2%	73.1%
0.5	65.4%	73.1%
1	69.2%	73.1%
4	81.0%	85.0%
6	75.0%	75.0%
12	70.0%	75.0%
24	65.0%	70.0%

5. Conclusions

The clinical results show that the Biowave System is safe, provides significantly better and longer lasting pain relief than TENS, and that the Biowave System provides pain relief for up to 24 hours for patients suffering from chronic low back pain.

6. Discussion Regarding Flawed Study Design

6.1 VAS Pain Measurements

For future studies, because patients had difficulty differentiating between "deep pain" and "surface pain," that only "pain" would be assessed using VAS measurements.

6.2 Treatment Duration

Subsequently it has been determined that a 30-minute duration Biowave treatment provides a greater magnitude of pain relief and longer lasting residual benefit than a 20-minute treatment. Therefore future studies will include 30-minute duration Biowave treatments instead of 20-minute duration Biowave treatments. Had this study included a 30-minute duration treatment in its design, Biowave would have provided even better results over TENS than those captured in this study.

6.3 Incorrect Electrode Size and Placement

Subsequently, it was discovered that the electrode placement design used in this study was flawed. It was originally thought that the Biowave electrodes needed to be in an opposing position to one another, hence one electrode on the abdomen and one over the pain site on the lumbar area of the back. Since the electrode placed on the abdomen is active and stimulation received over the abdomen is uncomfortable, patients complained that they couldn't increase the signal intensity to a high enough level for the pain site electrode on the back because the stimulation sensation felt on the abdomen prevented them from going higher.

If the Biowave electrode placement used two same sized independent electrodes to treat two locations of pain on the lower back, patients would have been able to increase the intensity to a much higher level which would have provided greater and longer lasting pain relief. Patients can tolerate a much higher intensity setting over the lumbar back than anywhere on the anterior of the torso. In future low back pain studies, the Biowave treatment will use two independent same sized electrodes over two locations of pain or over the origin of pain and the most proximal location of pain to the origin on the lumbar area of the back. Had this study included the proper electrode size and placement in its design, Biowave would have provided significantly better and longer lasting results as compared to TENS than those captured in this study.

6.4 Discussion Conclusions

Improvements to the study protocol design as described above would have resulted in the Biowave System having an even larger improvement and longer duration of pain relief versus TENS.

A Clinical Study of the Efficacy of the BioWave Device for Reducing Pain and Increasing Range of Motion Over 24 Hours Following a 20-Minute Treatment of Shoulder, Knee, Hip and/or Extremity Pain.

BioWave Corporation 510(k) August 15, 2005

A Clinical Study of the Efficacy of the Biowave Device for Reducing Pain and Increasing Range of Motion Over 24 Hours Following a 20-Minute Treatment of Shoulder, Knee, Hip and/or Extremity Pain.

This study was performed at the Coren Clinic in Norwalk, CT. The primary objective of the investigation was to evaluate the efficacy of the Biowave device for the relief of symptomatic shoulder, hip, knee or extremity pain. Efficacy was determined by comparing a patient's pre-treatment baseline pain score, utilizing the Visual Analog Scale (VAS), to his/her VAS pain score immediately following discontinuation of treatment, and at 6 and 24 hours following discontinuation of treatment.

The secondary objectives of the study were to demonstrate whether the Biowave device has a residual and/or cumulative effect in preventing the perception of pain and in providing an increase in Range of Motion (ROM) and to determine optimal pad size and pad placements for different treatment locations on the body.

The study was conducted on 22 patients and a total of 36 treatments were completed. The number of treatments received by each patient was randomized so that the patient was supposed to receive either three (3) treatments or one (1) treatment. Six (6) patients received a total of three (3) treatments each, two (2) patients received two (2) treatments each and fourteen (14) patients received 1 treatment each. Each treatment was separated by a minimum of 48 hours, but not by more than one (1) week. Feed Signal frequency settings were preset to 8.00 kHz and 8.122 kHz for all treatments. The beat frequency developed in the body was 122 Hz for all treatments. Patients were instructed to increase the power level on the device until they felt a strong and comfortable pressure sensation at the Pain Site Pad. Total treatment time was 20 minutes. Patients completed visual analog scale (VAS) and categorical pain assessments at baseline (before treatment), after 20 minutes of treatment (after the device was turned off and pads removed), and at 6 hours and 24 hours following the end of the treatment. Active range-of-motion (ROM) assessments were completed at baseline and after 20 minutes of treatment (after the device was turned off and pads removed).

All patients, 21 years of age or older, presenting to the clinic for symptomatic relief of shoulder, hip, knee or extremity pain were potential study candidates. Patients were selected without bias to gender, and must have been willing to comply with follow-up and post-treatment procedures. Patients were screened and who fulfilled all inclusion and no exclusion criteria were offered the opportunity to participate in the study. Those patients who subsequently fulfilled all inclusion criteria and no exclusion criteria and who provide study specific written informed consent were entered into the study. The patients must have had a score of ≥ 40 mm on the VAS pain scale for

their baseline pain score.

Patients were connected to the Biowave device by application of the Feed Pad to a location opposite their pain and a Pain Site Pad to a location directly over the pain site. For example, patients with pain on the front of their shoulder would have a Pain Site Pad placed on the front of their shoulder directly over the location from which the pain emanates. A Feed Pad would be placed on the back of the shoulder blade directly on the other side of the body (opposite) from the location of the Pain Site Pad. Feed Signal frequency settings were preset to 8.00 kHz and 8.122 kHz for all treatments. Beat Frequency settings were 122 Hz for all treatments. Patients were instructed to increase the power level on the device until they felt a strong and comfortable pressure sensation at the Pain Site Pad. If the sensation subsided slightly, patients were instructed to increase the power level until the strong and comfortable sensation returned. Patients made incremental increases in signal amplitude until they reached a steady state strong and comfortable pressure/tingling sensation that did not fade at the Pain Site electrode. Total treatment time was 20 minutes. Patients completed visual analog scale (VAS) and categorical pain assessments at baseline (before treatment), after 20 minutes of treatment (after the device was turned off and pads removed), and at 6 hours and 24 hours following the end of the treatment. Active range-of-motion (ROM) assessments were completed at baseline and after 20 minutes of treatment (after the device was turned off and pads removed). Vital signs were taken before and after each treatment session.

Results were analyzed for each treatment location on the body. The percentage of pain reduction was calculated by subtracting the post treatment VAS measurement from the baseline (before treatment) VAS measurement and dividing that result by the baseline VAS measurement. Range of motion (ROM) for flexion, extension, lateral movement, adduction and abduction was measured in degrees using a goniometer before and after the 20 minute treatment, and the percent increase in ROM was calculated.

The results are shown in Table 1 below and were evaluated as the follows:

- Median percent pain reduction for each location on the body and overall pain reduction immediately following the treatment, at 6 hours and at 24 hours post treatment
- Percent of Patients that achieved 50% or greater pain reduction immediately following the treatment, at 6 hours and at 24 hours post treatment.
- Median Percent increase in Range of Motion for each location on the body immediately following the treatment.

Table 1. Median Percent Reduction in VAS Scores Immediately Following Treatment and at 6 Hours and 24 Hours Post Treatment

Location	# of Treatments	# of Patients	% Pain Reduction 0 hours After Treatment	% Pain Reduction 6 hours After Treatment	% Pain Reduction 24 hours After Treatment
Elbow	4	2	65.9%	97.7%	94.1%
Foot	2	2	34.6%	37.0%	9.3%
Hip	5	3	65.1%	70.6%	56.8%
Knee	8	5	74.3%	62.6%	70.7%
Neck	3	1	52.2%	39.2%	38.5%
Shoulder	14	9	65.4%	55.1%	42.2%
TOTAL/MEDIAN	**36**	**22**	**64.7%**	**62.7%**	**56.8%**

Pain Reduction

The data from Table 1 above is also summarized in Figure 1 below. The median percent reduction in VAS pain scores across all treatments and all locations was 64.7% immediately following the 20-minute treatment, 62.7% at 6 hours and 56.8% at 24 hours. The elbow, hip, knee and shoulder treatments had the greatest level of efficacy, with neck treatments still showing positive results, but with not quite as strong a residual effect. As there are only two data points for the foot, no meaningful conclusion can be drawn.

P-values for the shoulder are as follows: vas 0hr $p<0.001$ n=13, vas 6hr $p<0.001$ n=13, vas 24hr $p<0.001$ n=13. P-values for the knee are: vas 0hr $p<0.001$ n=8, vas 6hr $p<0.003$ n=5, vas 24hr $p<0.02$ n=5. For the hip, p-values are: vas 0hr $p<0.01$ n=5. The population of VAS data for the hip at 6 and 24 hours, and for the elbow, foot and neck are too small to calculate meaningful p-values.

In general, initial indications for significant pain relief over 24 hours are positive for most locations on the body as shown below in Figure 1.

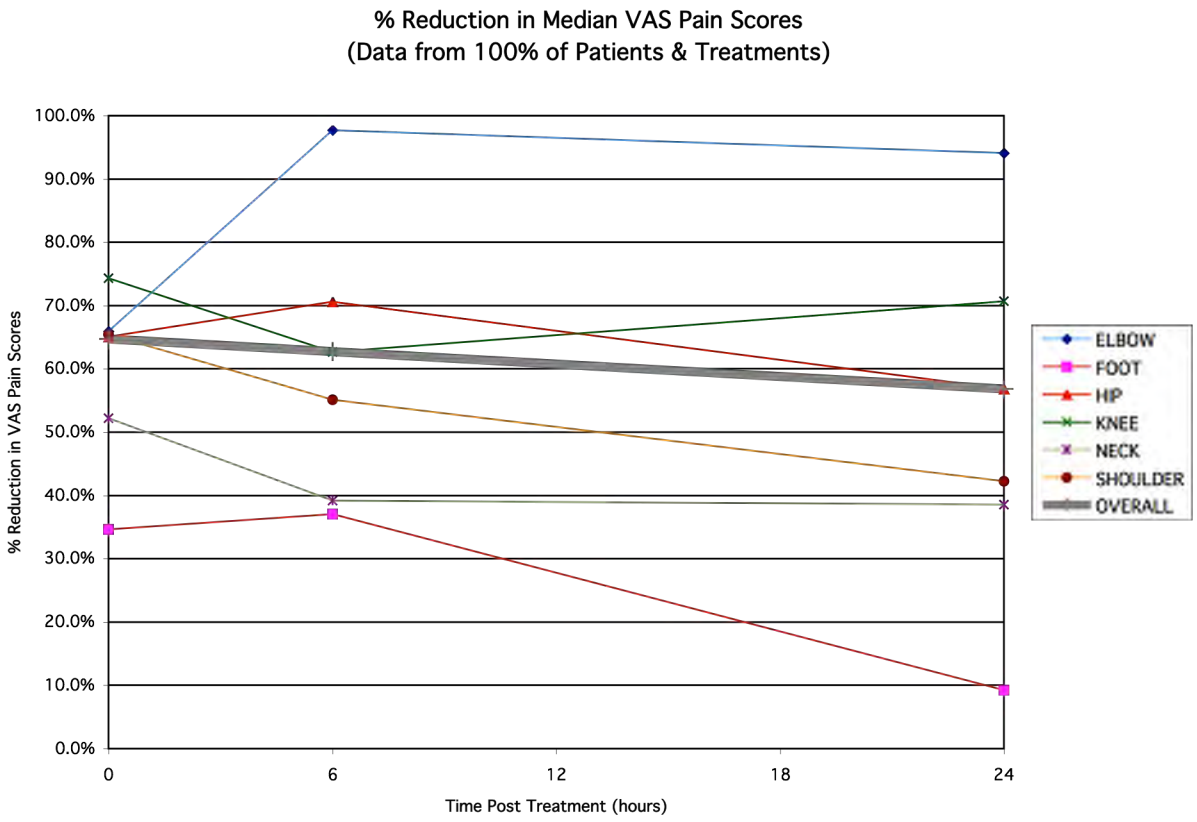


Figure 1. Percent Reduction in Median VAS Pain Scores

Percentage of Patients With Greater Than or Equal to 50% Pain Reduction

Most clinical studies focused on efficacy involving pain management devices rate the efficacy of a device based on the percentage of patients that achieve 50% or more pain relief. In comparing results from published clinical studies for the treatment of pain, Transcutaneous Electronic Nerve Stimulation (TENS) devices typically provide only 50% of the patients with an average 50% reduction in pain, only while the device is on. 50% of the patients receive no relief (less than 10% reduction in pain). The results for the Biowave device can also be seen below in Tables 2, 3 and 4 as well as graphically in Figure 2, which show the percentage of patients with 50% or greater pain reduction at 0 hours, 6 hours and 24 hours post treatment, respectively.

Table 2. Percent of Patients With 50% or Greater Pain Reduction at 0 Hours Post Treatment

Location	TOTAL # of Patients	# of Patients with > 50% Reduction in Pain	% of Patients with > 50% Pain Reduction 0 hours After Treatment
Elbow	4	2	50%
Foot	2	1	50%
Hip	5	4	80%
Knee	8	8	100%
Neck	3	2	67%
Shoulder	14	10	71%
TOTAL/MEDIAN	**36**	**27**	**75%**

Table 3. Percent of Patients With 50% or Greater Pain Reduction at 6 Hours Post Treatment

Location	TOTAL # of Patients	# of Patients with > 50% Reduction in Pain	% of Patients with > 50% Pain Reduction 6 hours After Treatment
Elbow	4	3	75%
Foot	1	-	0%
Hip	4	4	100%
Knee	5	4	80%
Neck	2	1	50%
Shoulder	13	7	54%
TOTAL/MEDIAN	**29***	**19**	**66%**

Table 4. Percent of Patients With 50% or Greater Pain Reduction at 24 Hours Post Treatment

Location	TOTAL # of Patients	# of Patients with > 50% Reduction in Pain	% of Patients with > 50% Pain Reduction 24 hours After Treatment
Elbow	4	4	100%
Foot	1	-	0%
Hip	4	3	75%
Knee	5	3	60%
Neck	2	1	50%
Shoulder	13	4	31%
TOTAL/MEDIAN	**29***	**15**	**52%**

***** Out of 36 Total Patients, 7 patients did not return to the investigator, the Case Report Forms with their VAS pain scores at 6 hours and at 24 hours post treatment. Therefore the Total Number of Patients at 6 hours and at 24 hours post treatment is 29 patients.

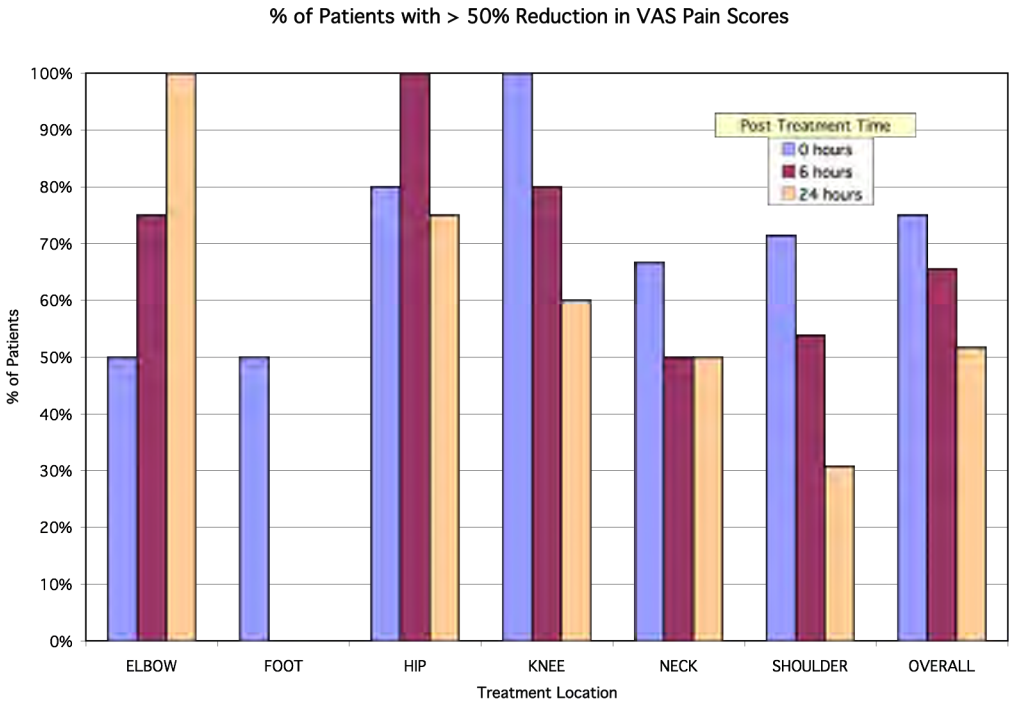


Figure 2. Percentage of Patients with > 50% Reduction in Pain

These results indicate that immediately following the Biowave treatment, the percentage of patients that received 50% or greater pain relief was 75% for all treatment locations (OVERALL) in comparison to TENS studies where typically only 50% of the patients receive a 50% or greater reduction in pain. Overall, at 6 hours post treatment, 66% of the patients still had a 50% or greater reduction in pain and at 24 hours post treatment, 52% of the patients had a 50% or greater reduction in pain. The results of this study show that a 20-minute treatment on the Biowave device provides continued pain relief at 0, 6 and 24 hours post treatment.

Range of Motion

Range of motion (ROM) for flexion, extension, lateral movement, adduction and abduction was measured in degrees using a goniometer before and after the 20 minute Biowave treatment, and the percent increase in ROM was calculated. All five ROM measurements are not applicable for all locations on the body. The types of measurements as well as the median percent increase (or decrease) in Range of Motion for each location on the body are presented in the table below. Median percent increase (or decrease) is derived from comparing a baseline reading immediately before the treatment to a reading immediately following the 20-minute treatment.

Table 5. Median Percent Increase in Range of Motion For Each Location on the Body Immediately Following the Treatment.

Location	# of Treatments	% Increase/ (Decrease) in Flexion	% Increase/ (Decrease) in Extension	% Increase/ (Decrease) Laterally	% Increase/ (Decrease) in Adduction	% Increase/ (Decrease) in Abduction
Elbow	4	35.1%	11.5%			
Foot	2	-10.8%	-9.0%			
Hip	5	29.6%	46.7%	65.4%		
Knee	8	15.4%	5.8%			
Neck	3	30.0%	18.2%	19.0%	12.5%	6.7%
Shoulder	14	5.4%	16.0%	26.4%	34.0%	5.9%

Range of motion (ROM) increase is statistically significant for the shoulder, knee and hip. There were not enough data points from the other locations on the body to draw any meaningful conclusion.

For the shoulder p-values were: flex $p<0.003$ $n=14$; ext $p<0.002$ $n=14$.

For the knee p-values were: flex $p<0.02$ $n=8$; ext $p<0.09$ $n=8$ significance would be much better with a larger sample size.

For the hip, p-values were: flex p=N.S. $n=5$, the sample size is too small; ext $p<0.08$ $n=5$ significance would be much better with a larger sample size.

The following have too small a population of ROM data to report: elbow, foot, neck and shoulder adduction and abduction.

ROM data is also presented in graphical format below in Figure 3 below.

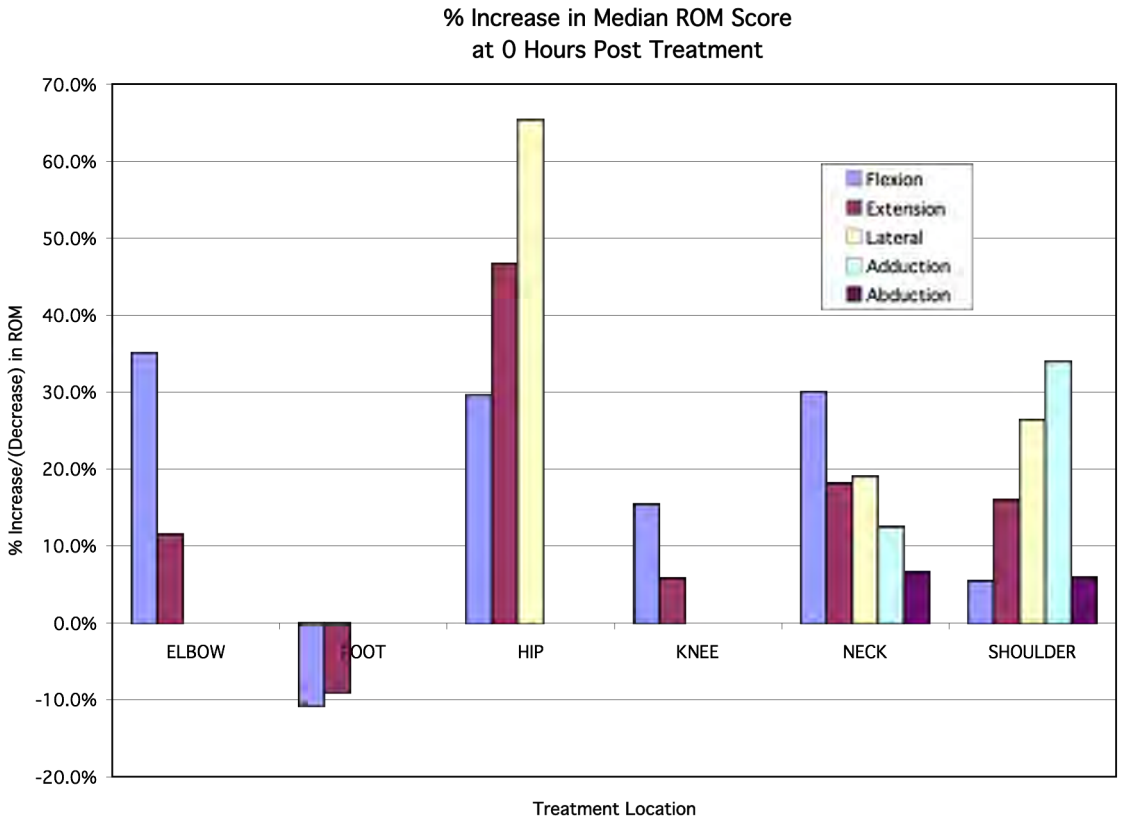


Figure 3. % Increase in Median ROM Score at 0 Hours Post Treatment

Adverse Events

One female patient experienced an extended tingling sensation in her shoulder, following her first treatment, which lasted for about 60 minutes after the device was turned off. One male patient experienced an extended tingling sensation in his hip, following his first treatment, which lasted for about 15 minutes after the device was turned off. Neither patient complained about the tingling and both patients still rated the treatment "excellent". Neither patient had residual tingling from their subsequent treatments. The female patient operated the device at slightly lower signal amplitudes for her second and third treatments. The male patient actually operated the device at higher signal amplitudes for his second and third treatments as compared to his first treatment.

Conclusion

This study shows that the Biowave device is an effective treatment for relieving shoulder, hip, knee, and neck or elbow pain. Median VAS scores, based on all data points, at the end of the 20-minute treatment, and at 6 and 24 hours following the treatment were significantly below the baseline VAS score for all locations tested on the body. The median percent reduction in pain

across all data points following the treatment were 65% at 0 hours, 63% at 6 hours and 57% at 24 hours post treatment.

The study also shows that the percentage of patients that experienced a 50% or greater reduction in pain using the Biowave device is statistically significantly better than published TENS results. Immediately following the Biowave treatment the percentage of patients that received 50% or greater pain relief was 75% which is significantly better than reported TENS studies where typically only 50% of the patients receive 50% or greater reduction in pain. For Biowave at 6 hours post treatment, 66% of the patients still had a 50% or greater reduction in pain and at 24 hours post treatment, 52% of the patients had a 50% or greater reduction in pain. The Biowave device had greater efficacy at 0, 6 and 24 hours post treatment as compared to published TENS results at 0 hours post treatment demonstrating that the Biowave device provides 24 hours of residual pain relief.

The above clinical studies demonstrate that the Biowave device provides pain relief for up to 24 hours post treatment. Since there are very few published studies regarding TENS devices and extended pain relief, Biowave Corporation demonstrated that the Biowave device provided greater extended pain relief in comparison to the TENS device in phase 3 of the Weill Medical College Study at Cornell University/New York Presbyterian Hospital.

Evaluation of optimal signal frequency and efficacy of BioWave

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ISSN 0003-2999 Volume 96, Number 2S, February 2003 Supplement to Anesthesia &Analgesia

ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society, the Society of Cardiovascular Anesthesiologists, the Society for Pediatric Anesthesia, the Society for Ambulatory Anesthesia, the International Society for Anaesthetic Pharmacology, and the Society for Tecnology in Anesthesia

Abstracts of Posters Presented at the International Anesthesia Research Society
77th Clinical and Scientific Congress
New Orleans, LA • March 21-25, 2003

S-213

SYMPTOMATIC TREATMENT OF CHRONIC LOW BACK PAIN: DETERMINATION OF OPTIMAL SIGNAL FREQUENCY AND PRELIMINARY EFFICACY OF A TARGETED NON-INVASIVE ELECTRONIC PAIN CONTROL DEVICE

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INTRODUCTION: The Biowave System (Biowave Corporation, Norwalk, CT) introduces two premixed high frequency wave forms (feed signals) through an electrode placed on the skin opposite the pain site (feed electrode). The electric field contains a low frequency component (beat frequency) equal to the difference between the feed signals. The feed signals pass through the body to a second electrode at the treatment site (pain site electrode). The feed signals mix, yielding an electric field equivalent to the beat frequency component, which is believed to interrupt transmission of pain impulses by preventing action potential propagation along pain fibers. This technology is being explored as a novel therapy for treating chronic, acute or post-surgical pain.

METHODS: Volunteers consented to undergo 3 treatment sessions in either of 2 phases with varying beat and feed frequencies separated by at least 24 hours. Criteria for inclusion: age 18-60, low back pain (below T12) for >3 months without radiation, and Visual Analog Scale (VAS) pain score of ≥4 out of 10 at screening. Exclusion criteria were pregnancy, presence of a pacemaker or other implantable devices, cardiac arrhythmias, epilepsy, low back surgery, alcohol or drug abuse, or significant medical or psychological conditions. Subjects were connected to the Biowave device by application of a large hydrogel feed electrode (12.7 cm x 20.3 cm) to the abdomen and a smaller pain site electrode (5.1 cm diameter) to the lower back over the source of the pain. Subjects increased the power output of the device until strong tingling/pressure was felt; treatment continued for 20 min. Patients completed VAS pain assessments at baseline, after 20 min of treatment, and at 10 and 30 min after the device was turned off.

RESULTS: 29 patients were enrolled; at least 3 subjects completed each group. The only adverse reaction observed was skin irritation and minor blistering on one patient at the pain site electrode (n=1).

Feed Freq. (kHz)	Beat Freq. (Hz)	n	VAS Rating Baseline	VAS Rating @20 min	VAS Rating @30 min	VAS Rating @50 min
Phase 1						
8	122	3	4.9±0.8	2.5±1.6	2.6±2.2	1.7±0.8
13.33	122	8	6.7±1.5	4.3±3.0	2.8±1.7**	2.6±2.2**
26.8	122	5	5.7±0.6	2.6±0.8**	1.6±1.3**	2.0±2.2**
Phase 2						
8	90	7	5.3±1.0	2.3±2.1*	1.9±1.1**	3.3±2.5
8	122	3	5.0±1.3	1.6±0.7*	2.6±1.6	0.9±0.4*
8	150	3	5.9±1.8	3.6±2.7	1.8±2.5	0.9±1.1

*p<0.05, **p<0.01 vs. baseline by ANOVA with Dunnett's post-hoc test.

DISCUSSION: At a beat frequency of 122 Hz, all 3 feed frequencies tested produced comparable analgesia as evidenced by >50% reductions in VAS at 30 minutes post-treatment (VAS Rating at 50 min). Variations in beat frequency at a feed frequency of 8 kHz showed significant pain reductions for 122 and 150 Hz, particularly at 30 minutes post-treatment (VAS Rating at 50 min). Analgesia persisted for at least 30 min after the treatments. Further studies are warranted to confirm the efficacy and safety of the system, as well as the duration of analgesia. The data suggest that the Biowave System is effective in the symptomatic treatment of chronic low back pain.

Supported by a grant from Biowave Corporation.