Journal of Pain Research

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ORIGINAL RESEARCH

Retrospective Evaluation of Bipolar Peripheral Nerve Stimulation for Nociceptive and Neuropathic Pain: A Pilot Study

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Purpose: This retrospective review evaluates pain and patient-defined functional goal improvement utilizing bipolar peripheral nerve stimulation (PNS) in chronic neuropathic and nociceptive pain states.

Patients and Methods: Our dataset includes 24 patients who underwent implantation of a permanent peripheral nerve stimulator from January 2018 through December 2022. A total of 29 leads were implanted amongst 24 patients, with 5 patients having leads at 2 different dermatomes. Fifteen leads were placed for primarily neuropathic pain, and 14 leads were placed for nociceptive pain. Inclusion criteria were the following: pain duration greater than 6 months, documented peri-procedural Numerical Pain Rating Scale (NPRS) and greater than 60 days follow-up post implant.

Results: Data was collected and analyzed showing that 89.6% of implants at 6 months follow-up and 70% at 12 months follow-up achieved 50% or greater pain relief. A significant reduction in NPRS scores when comparing pre-procedure pain scores (Median = 7, n = 29) to 6-month follow-up data (Median = 2, n = 29), $p<0.001$ with a large effect size, $r = 0.61$. Ninety-three percent of patients reported achieving their personal functional goal. Twelve of the fourteen (86%) leads implanted for primary nociceptive pain and fourteen of the fifteen (93%) leads implanted for neuropathic pain achieved ≥50% relief at 6 months. At twelve months, seven leads in each group provided ≥50% sustained pain relief. Of the 14 patients that were on opioids, 6 discontinued, while another 2 had a reduction in oral morphine milligram equivalents (MME) at the 12-month follow-up.

Conclusion: This retrospective review demonstrates the potential clinical application of PNS in both nociceptive and neuropathic pain states. Further prospective studies are warranted to validate the effectiveness of PNS in the treatment of refractory nociceptive and neuropathic pain states.

Keywords: peripheral nerve stimulation, neuromodulation, neuropathic pain, nociceptive pain, chronic pain

Introduction

Peripheral nerve stimulation (PNS) was introduced in 1967 as a treatment for patients with cutaneous, sensory or nerve root pain.[1] PNS has been used successfully to treat a multitude of primarily neuropathic chronic pain conditions of peripheral origin,[2] complex regional pain syndrome,[3] chronic headache,[4] neuropathic post-surgical pain syndromes,[5,6] and mechanical low back pain.[7] Over the past 50 years, there have been significant PNS system hardware and software advances to target refractory neuropathic and mixed pain disorders. Neuropathic pain classically presents with burning, electric shocks, pins and needles, tingling, numbness, or itching with physical examination showing hypoesthesia to touch or pinprick. On the other hand, somatic nociceptive pain may be sharp, stabbing, dull, or aching and is often well localized. Physical examination typically includes restricted range of motion and worsening pain with mechanical loading or provocative examination maneuvers. When compared to neuromodulation of central neural targets, PNS confers an advantage of achieving focal analgesia along an intended cutaneous area of innervation. Historically, a neurostimulator lead array was placed via an open

Received: 7 May 2024
Accepted: 30 July 2024
Published: 5 September 2024

surgical technique to directly visualize the target peripheral nerve(s) and allow accurate adjacent lead placement. The electrode was connected to a rechargeable or primary cell internal pulse generator to deliver electrical stimulation. The invasive nature of this approach, potential surgical complications, restrictions for future magnetic resonance imaging (MRI) scanning, lack of prospective data and insurance payer coverage limited its use for many years.

Over the past decade, there has been a resurgence of interest in PNS. This is primarily due to the advances in ultrasound guided percutaneous lead placement, waveform technology, smaller generator sizing, improved MRI-conditional labeling, and robust data observations. Additionally, the development of tailored peripheral nerve lead designs with tines that minimize lead migration and the use of wireless external generators have improved the practicality and durability of this therapy. Finally, PNS implants utilizing these new systems are commonly performed in an outpatient setting with local anesthesia or intravenous sedation, which has greatly increased adoption of this therapy.

It is important to make a distinction between peripheral nerve field stimulation (PNFs), transcutaneous electrical nerve stimulation (TENs), and peripheral nerve stimulation (PNS) of a named nerve. PNFs is a minimally invasive procedure where electrodes are placed subcutaneously to stimulate cutaneous afferents,[8,9] and connected to an implanted pulse generator, whereas TENs is delivered through a non-invasive external unit producing strong, but comfortable, paresthesia.[10,11] PNS involves placement of a percutaneous lead adjacent to a named nerve under direct ultrasound visualization or near well-established anatomic targets using fluoroscopic guidance. This lead is either connected to an implantable pulse generator, or an external pulse generator (EPG) on a temporary (up to 60 days), or permanent basis.

The only temporary 60-day stimulation system (SPR Therapeutics) available uses monopolar stimulation whereby energy is delivered from a single electrode and the circuit is completed via a small dispersive pad. Meanwhile, all commercially available permanent PNS systems offer a multi-contact bipolar design that delivers energy from anode to cathode resulting in depolarization at the cathode and hyperpolarization at the anode. This is an important distinction since there is a lack of data demonstrating a correlation between the clinical outcomes using temporary monopolar versus permanent bipolar peripheral nerve stimulation. At the time of this publication, a specifically designed trial lead delivering bipolar stimulation is not available prior to permanent system implant. In this study, we examine the outcomes of a permanent bipolar PNS system on improvement of both neuropathic and nociceptive pain.

Materials and Methods

This retrospective study was conducted after submission to Advocate Aurora Health Institutional Review Board (IRB), which considered it an exempt research project and waived the need for consent (20–241ET). Declaration of Helsinki guidelines were followed, and patient records were reviewed retroactively. All patient data was stored and secured in a safe database. This study included 24 consecutive patients that had a successful ultrasound guided local anesthetic nerve block and were implanted with a permanent peripheral nerve stimulator system (StimRouter, Bioventus, Valencia, CA, USA) between January 2018 and December 2022. A successful nerve block was defined as 50% or greater reduction of pain on the Numerical Pain Rating Scale (NPRS). All nerve blocks were conducted with 3 mL of Lidocaine 2%. Five of our patients had a lead implanted at two different dermatomes bringing the total number of implants to 29 (Figure 1). Inclusion criteria were patients implanted with StimRouter PNS and had well-documented pre-procedure and six-month follow-up pain scores. We also included patients' self-reported perceived functional improvement and overall satisfaction with PNS. Perceived functional improvement was a pre-defined patient goal that was documented in the medical record. Some patient-specific goals were being able to water the lawn, lift their arm over a car steering wheel and drive with less pain, reducing or discontinuing opioids, and getting dressed in less pain. Pain relief at 6 months post PNS implant served as the primary endpoint, while follow-up data from 12 months served as the secondary endpoint.

Patient demographic information including age, sex, BMI, history of tobacco use, history of previous surgeries at the implant site, history of opioid consumption, and pain duration were collected from the electronic medical records (EMRs) (Table 1). Regular use of opioids pre and post PNS implants were reviewed from EMRs. Regular use of opioids in this study was defined as patients taking any morphine milligram equivalents (MME) during the last 60 days prior to implant on a daily or as needed basis for their chronic pain. A Wilcoxon signed rank test was used to assess the statistical significance and effect sizes between pre-implant and post-implant NPRS scores at 6 and 12 months (SPSS, IBM, Armonk, NY).

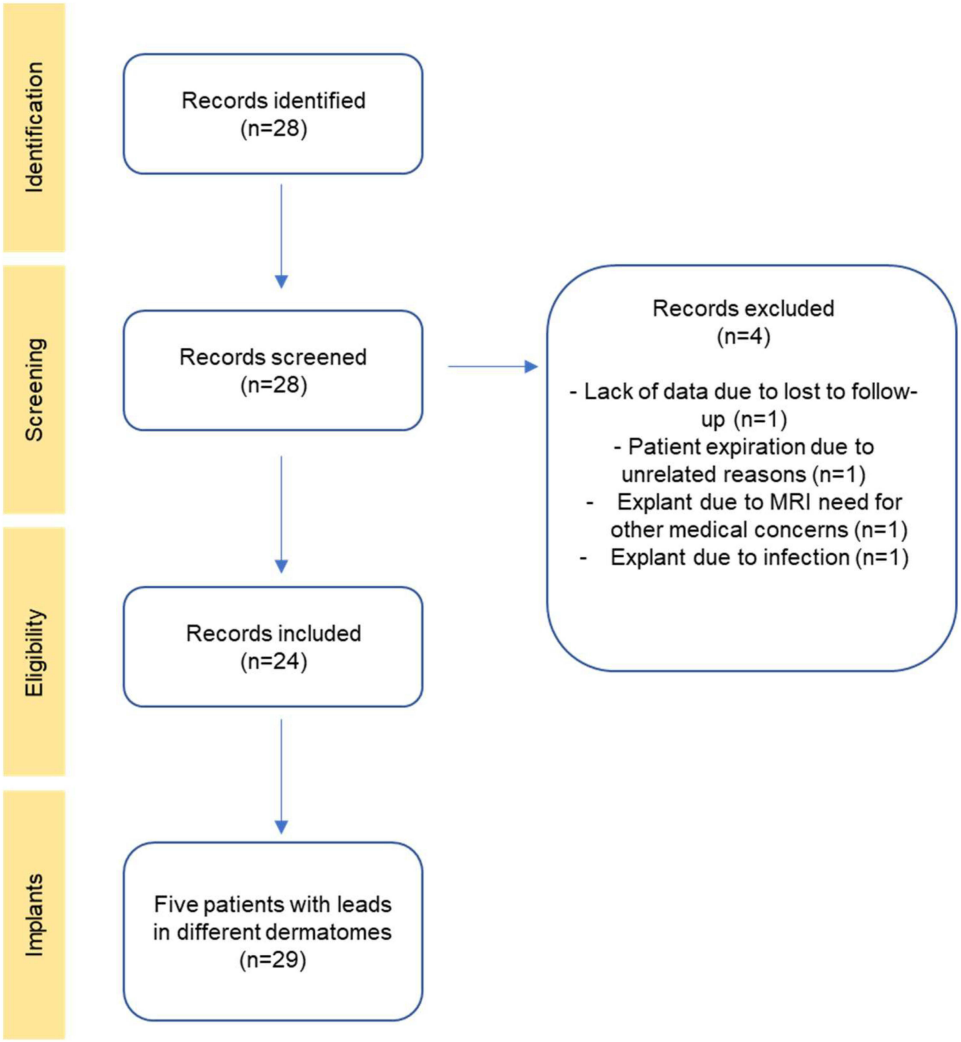

Figure 1 Study Flow Diagram.

Results

Data from 29 PNS implants were collected and analyzed for 24 patients (Table 1). There were 9 males (37.5%) and 15 females (62.5%) with an average age of 59.2 years and average pain duration of 4.8 years. Seven of our patients had a pain duration of minimum 10 years. Average BMI of the patients was 35.3 kg/m^2. NPRS pain scores were reported at pre local anesthetic nerve block visit, 6 and 12 months post-PNS implant follow-up. Average follow-up time for the primary end point was 168 days and 526 days for the secondary end point. Individual nerve targets are shown in Table 2.

A Wilcoxon signed rank test revealed a significant reduction in NPRS scores when comparing pre-procedure pain scores (Median = 7.00, n = 29) to 6-month follow-up data (Median = 2.00, n = 29), $z = -4.62$, $p < 0.001$ with a large effect size, $r = 0.61$ and to 12-month follow-up (Median = 2.75, n = 20), $z = -3.922$, $p < 0.001$ with a medium effect size, $r = 0.56$ (SPSS, IBM, Armonk, NY). Fourteen of the twenty-nine leads (48%) were implanted for primary nociceptive pain and fifteen of the twenty-nine leads (52%) were implanted for neuropathic pain (Figure 2). At 6 months, 89.6% of implants achieved ≥50% pain reduction in their respective dermatomes (n = 26 out of 29 total implants) (Figure 3). Twelve of the fourteen leads that were implanted for primary nociceptive pain provided ≥50% relief at 6 months follow-up, one achieved more than 40% pain relief and one did not provide relief. Fourteen of the fifteen leads placed for neuropathic pain provided ≥50% pain relief at 6 months.

Table 1 Patient Demographics and Baseline Characteristics

Variable	Number Reported
Patients included	24
Total implants	29
Age	
Mean (SD)	59.2 (16.3)
Sex	
Male	9
Female	15
BMI in kg/m²	
Mean (SD)	35.3 (11.7)
≥30	14
Tobacco use	
Current	5
Never	11
Former	8
Pain duration in years	
Mean (SD)	4.8 (4.9)
≥10	7
Diagnosis	
Nociceptive	14
Neuropathic	15
Previous surgery at implant site	
Yes	22

Abbreviations: SD, standard deviation; BMI, body mass index.

Table 2 Nerve Targets

Target Nerve	Count
Saphenous	12
Suprascapular	7
Genitofemoral	2
Ulnar	2
Sural	1
Tibial	1
Superolateral Genicular	1
Common Peroneal	1
Sciatic	1
Femoral	1

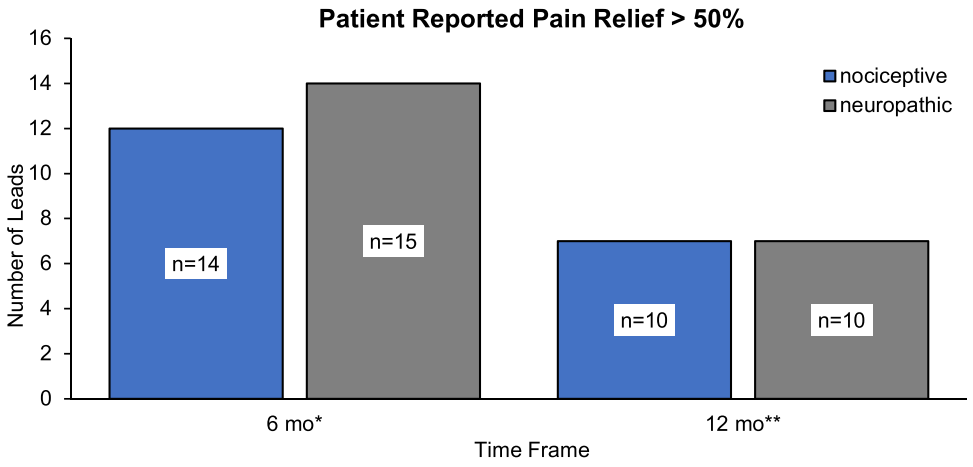

Figure 2 Breakdown of treatment success for nociceptive and neuropathic pain states at various time intervals following device implant. Treatment success is defined as 50% or greater reduction in pain intensity as measured through NPRS (*average duration 168 days, **average duration is 526 days).

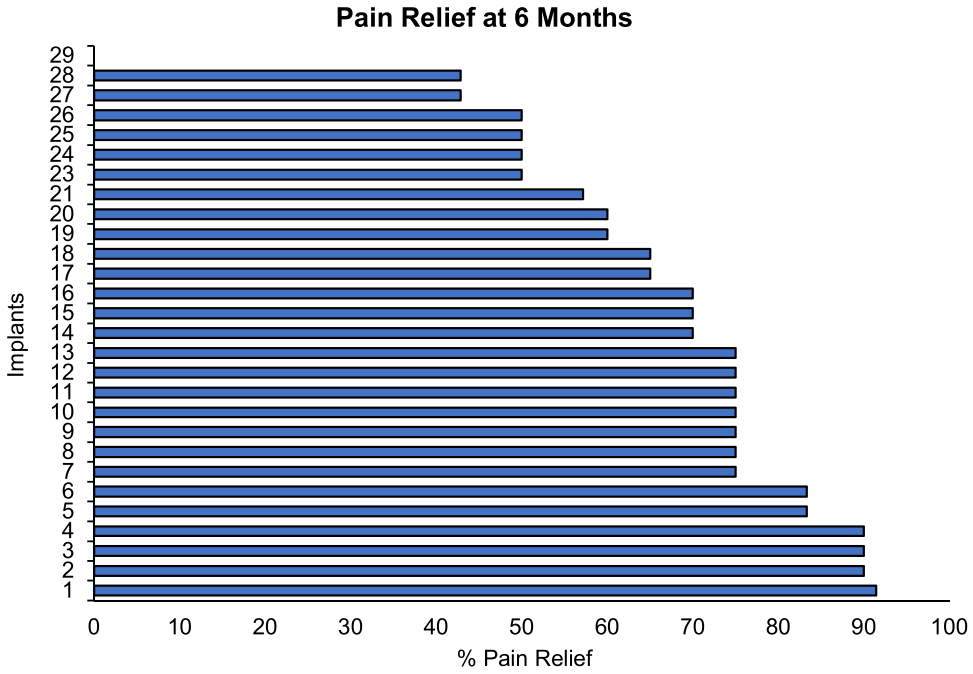

Figure 3 Change in patient reported pain scores six months following implants (average duration is 168 days).

At 12-months data were available for 20 leads. Seven of ten leads for neuropathic pain (70%) and seven of the ten leads for nociceptive pain (70%) provided ≥ 50% reduction in pain (Figure 4). In two patients with nociceptive pain, one lead did not provide any relief, while another was explanted following a motor vehicle collision. Of the fourteen patients that used opioids, six discontinued the use of prescription opioids at 12 months, while two other patients reduced their daily total MME use.

Discussion

The results presented in this retrospective review highlight the efficacy of an implanted bipolar peripheral neuromodulation system in both nociceptive and neuropathic pain. In this cohort, 89.6% of leads achieved ≥ 50% pain reduction at their follow-up at 6-months (average 168 days), and 93% of the patients were satisfied with therapy and subjectively reported achieving a personal functional goal.

The stimulation was delivered in four-hour treatments up to three times daily. Of note, 5 of our patients had received temporary stimulation with a monopolar output system prior to implantation with this bipolar system. Three of these

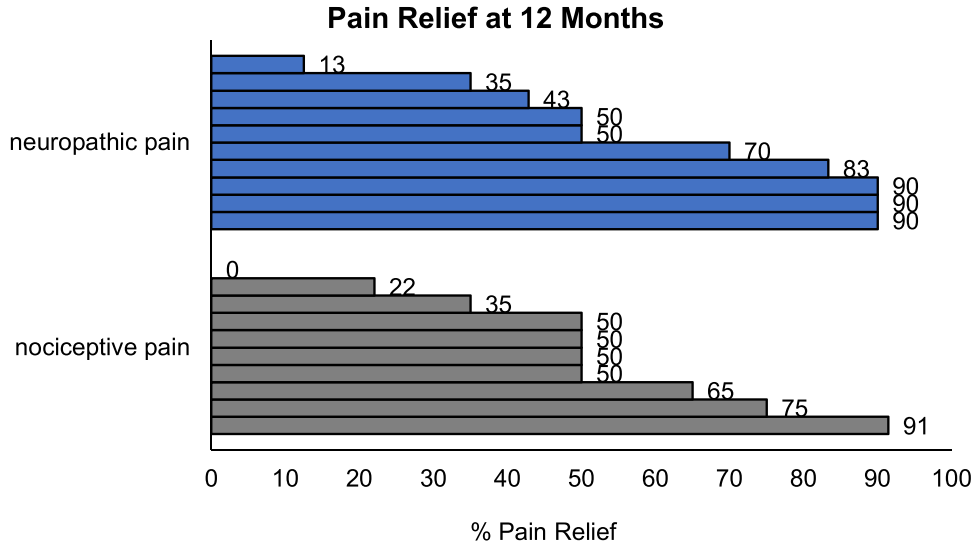

Figure 4 Percentage pain relief for leads with 12 months follow-up data (average duration is 526 days).

patients reported 90% relief and two patients reported greater than 50% relief, which was similar to what they experienced using the monopolar system. To date, there is no prospective study that evaluates the success of permanent bipolar implant in patients that had undergone a monopolar treatment first.

A prospective, randomized, double-blind, crossover study for this device described ninety-four patients with severe intractable neuropathic pain that were implanted and randomized to treatment (n = 45) or control (n = 49). A responder to therapy was defined as achieving 30% reduction in pain without an increase in pain medication. At 3 months 38% of the patients were responders in the treatment arm when compared to 10% in the control arm, which was statistically significant. The reduction in pain in the treatment group was 27.2% when compared to 2.3% reduction in the control group. At three months, crossover to the treatment group was offered to the control group, and thirty-nine out of forty-five patients opted to crossover. Of these patients 30% (n = 9) were responders to treatment.[2] The reduction in pain in our cohort is perhaps more profound due to advancements in ultrasound guided placement when compared to this randomized control clinical trial.

The exact mechanism of action (MOA) of PNS is unknown but postulated to have both peripheral and central mechanisms.[12,13] The gate control theory first described by Melzack and Wall in 1965 is the foundation of future work on mechanism of action. They proposed that activation of large diameter Aβ sensory fibers suppresses neural activity in small diameter nociceptive afferents in the spinal dorsal horn.[14] The sustained benefit from PNS likely stems from downregulation of maladaptive neuroplasticity in the peripheral and central nervous systems. Preclinical and clinical data have shown reduction in pain and improvement in physiological recovery with peripheral nerve stimulation.[15–17]

Unlike spinal cord stimulation, a clearly defined algorithm for trialing PNS prior to temporary (eg: 60-day) or permanent placement does not exist. Many physicians choose to isolate a neural target by performing an ultrasound guided local anesthetic nerve block. While the predictability of this method in identifying the implicated nerve(s) may be high, the correlation to relief following PNS implant is difficult to ascertain. A recent review evaluating diagnostic blocks and PNS outcomes at 3 and 6 months did not find a difference when compared to those not receiving blocks before PNS implant.[18] This is in part due to the fundamental differences in mechanism of action between local anesthetics versus peripheral nerve stimulation. Local anesthetics suppress action potential in excitable tissues by reversibly binding to Na+ channels, whereas stimulation has long been believed to activate motor or sensory fibers as opposed to blocking conduction.[19,20] The limitation of this approach is that patients that may have benefitted from PNS due to its distinctive mechanism of action were excluded on the basis of a failed nerve block. Our patients received ultrasound guided nerve blocks as part of their diagnostic workup. Other trialing methods include performing paresthesia mapping using a stimulating needle or catheter or utilizing a spinal cord stimulator lead. Alternatively, the local anesthetic block may be omitted, and a temporary sixty-day treatment utilizing a monopolar system may be chosen. There is significant

prospective and retrospective data demonstrating durable pain relief beyond sixty days of stimulation.[6,7,21] In the subset of patients without sustained after temporary stimulation, a permanent implant may be considered.

The two most common targets in this cohort are chronic knee and shoulder pain. The knee receives complex innervation primarily from the articular branches of the femoral, sciatic, and obturator nerves.[22] The infrapatellar branch of the saphenous nerve (IPSN) is believed to be the culprit for persistent anterior and anteromedial knee pain. IPSN is a purely sensory nerve that crosses the inferior knee from medial to lateral and innervates the skin below the patella as well as anterior inferior knee capsule.[23] PNS may be considered in patients with refractory non-surgical osteoarthritic knee pain who failed to improve with physical therapy, viscosupplementation/corticosteroid injections, and genicular nerve radiofrequency ablation. We targeted the saphenous nerve in the adductor canal for both neuropathic and nociceptive pain from osteoarthritis with success.

The shoulder innervation primarily comes from the suprascapular and axillary nerves. The suprascapular nerve is a branch of the upper trunk of the brachial plexus and provides motor supply to the supraspinatus and infraspinatus muscles and sensory innervation to the posterior and superior joint capsule, glenoid, acromion, and posterior scapula. The axillary nerve is a terminal branch of the posterior cord and supplies innervation to the anterior-inferior and posterior-inferior joint capsule. There are multiple case reports and case series that show the benefit of PNS for post-stroke shoulder pain, causalgia, and multifactorial chronic intractable shoulder pain.[24–28] The results reported in our case series are consistent with findings reported in the literature.

We are aware of several limitations that exist in our study. This is a retrospective, single-center study, which limits the generalizability of the obtained results, in addition to the small sample size. Our measures of self-improvement were based on chart review and self-defined goals, instead of validated questionnaires (PROMIS, PGIC, etc.), which measure functional and psychosocial measures of improvement. Additionally, the length of post-procedure follow-up data poses another limitation. While we include standard 6- and 12-month follow-up data, obtaining data for a longer period, such as 24-month follow-up, may bolster the strength of our data. We do not report the stimulation parameters for each patient as this data was not readily available. Finally, our study lacks a control group, which may introduce potential biases and limit the comparison of our study group to other interventional modalities.

Conclusion

Peripheral nerve stimulation is a minimally invasive, safe, and effective treatment for chronic refractory pain of neuropathic origin. Within the limitations of this study, we observed similar efficacy of PNS for nociceptive pain, however prospective data with long term follow-up is needed to support use for this indication.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

No external funding was obtained for this study. Aurora Health Care Foundation provided the funds to cover the article processing fees.

Disclosure

MMA is a consultant for Abbott laboratories, SPR therapeutics, Bioventus, Medtronic, and Vertos. AM is a consultant for Boston Scientific. YMI, MBF and AC have no conflicts of interest.

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