Journal of Pain Research

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CLINICAL TRIAL REPORT

Safety and Efficacy of Axon Therapy (SEAT Study), Utilizing Magnetic Peripheral Nerve Stimulation (mPNS) for Treatment of Neuropathic Pain

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Background: Many of the current treatments for chronic neuropathic pain have variable effectiveness and known side effects. Given the prevalence of this type of intractable pain (3–17% of general population), additional therapeutic non-invasive approaches are desired. Magnetic Peripheral Nerve Stimulation (mPNS) delivered at 0.5Hz provides an effective pain relief without side effects. The objective of this randomized, controlled, multi-site clinical trial was to compare long-term safety and efficacy of mPNS in patients with chronic, intractable, post-traumatic or post-surgical neuropathic pain to comprehensive Conventional Medical Management (CMM).

Methods: A total of 65 patients with post-traumatic, post-surgical neuropathy were treated within a multicenter, randomized, clinical trial comparing the safety and effectiveness of mPNS + CMM to CMM alone. Patients were randomized 1:1 and followed through 90 days. The primary endpoint is a proportion of responders, 50% or greater reduction in pain at Day 90. The secondary endpoints included the European Quality of Life 5 Dimensions 3 Level (EQ-5D-3L) and Patient Global Impression of Change (PGIC).

Results: At 3 months, 71% of subjects were considered responders (>50% pain relief) in the mPNS + CMM group vs 13% of subjects in the CMM group. The mPNS + CMM group had a mean reduction in VAS scores at Day 90 of 3.8 points (>50% reduction), while CMM showed less than a 1-point (0.7 point) mean reduction or ~10% reduction ($p < 0.0001$). The EQ-5D-3L score increased in the mPNS + CMM study group, whereas the CMM group showed no improvement in EQ-5D-3L at Day 90. PGIC responder rates were 80.6% and 4.3% at Day 90 for mPNS + CMM and CMM groups, respectively.

Conclusion: mPNS + CMM was superior to CMM in a randomized prospective study when used for treatment of post-traumatic, post-surgical neuropathy. Due to the lack of other effective non-invasive treatments for neuropathic pain, mPNS should be considered much earlier in the treatment algorithm.

Keywords: neuropathic pain, noninvasive, cost effective, pain relief, neuropathy

Introduction

There is a substantial clinical need for improved treatments for chronic neuropathic pain. Chronic neuropathic pain impacts most aspects of a person's life, including emotional distress and/or social impairment.[1] Unfortunately, currently available treatments have limited effectiveness in most subjects with severe chronic pain. Opioid analgesics, antidepressants and membrane stabilizers are frequently prescribed despite very high (between 4 and 8 patients tried in order to have one achieving more than 50% of pain relief) NNT (number needed to treat) scores.[2]

More aggressive therapeutic approaches include nerve denervation or an implant of neuromodulation devices, like with subcutaneous peripheral nerve stimulation, and lack the evidence on the longevity of such therapies.[3]

Received: 8 June 2024
Accepted: 12 September 2024
Published: 28 September 2024

Magnetic Peripheral Nerve Stimulation is FDA-cleared to treat chronic and intractable post-traumatic and post-surgical pain. mPNS delivers a series of biphasic, time-varying magnetic pulses which induce strong electrical fields in the nerve bundles located in the region of the center of the waveform.[4] mPNS delivers these pulses at a frequency in the range of 0.2 to 5Hz, with typical application of 0.5Hz.[4] The objective of these relatively low-frequency pulses is to induce action potentials and neuronal activity in both the ascending and descending pathways of both the peripheral and central nervous systems.[5]

Magnetic PNS is not painful to patients. This is due to the basic physics of the induced fields and the differential recruitment of nerve fibers within a bundle. mPNS recruitment has been shown to be proportional to the inverse square of the fiber diameter.[6] A typical fiber diameter ratio of A-beta (sensory) to A-delta (pain fibers) is 3:1, therefore the recruitment ratio between A-beta to A-delta, respectively, is 9:1. For electrical PNS or TENS, it has been shown that, for fibers near the size of A-beta, recruitment is proportional to the inverse of the fiber diameter.[7] The recruitment ratio is therefore 3:1, indicating a higher proportion of A-delta recruitment that often needs to be optimized and A-beta recruitment being reduced given the pain tolerance of the patient.

mPNS is applied in discrete 13.33-minute sessions, with a session protocol of 3 sessions in Week 1, weekly in Weeks 2–4 and bi-weekly in Weeks 5–13. The amount of motor nerve recruitment is an additional therapeutic optimization available to the practitioner. It has been proposed that motor activity in both the ascending and descending pathways of the PNS and CNS can lead to an increased rate of plasticity changes in the brain as afferent neuronal signals are suppressed.[5] Competitive therapeutic solutions such as percutaneous electrical PNS or implanted SCS must operate below the motor threshold or patient discomfort may occur.[8] Additionally, neuromodulation using ultra low frequency current waveform (0.5–10Hz) reversibly blocks axonal conduction and chronic pain.[9]

A study of pragmatic design to compare mPNS + CMM therapy to traditional CMM as applied in normal clinical practice is required to understand these potential benefits. Specifically, this multicenter, randomized, controlled, clinical trial (the SEAT study) compared the safety and efficacy of mPNS to traditional CMM in patients with chronic neuropathic pain (ClinicalTrials.gov identifier: NCT04795635). Here, we present the three months primary and secondary outcomes from this trial.

Methods

Study Design and Population

This prospective, randomized, controlled trial was designed to compare the long-term safety and efficacy of mPNS therapy in patients with chronic, intractable, post-traumatic or post-surgical neuropathic pain to Conventional Medical Management (CMM). The study was conducted in compliance with the US Code of Federal Regulations and recommendations guiding physicians in biomedical research by the 18th World Medical Assembly, Helsinki, Finland. The study protocol and informed consent forms were approved by the Central Institutional Review Board (Western Institutional Review Board (WIRB)-Copernicus Group (WCG® IRB), Puyallup, Washington.

Consenting patients were assessed for eligibility based on inclusion and exclusion criteria and randomized across four comprehensive pain treatment centers in the United States. Key inclusion criteria were chronic, peripheral neuropathic pain, refractory to conservative therapy for a minimum of 3 months (previous conservative treatments included pain medications, physical therapy, spinal and/or peripheral nerve injections, pharmacological, and behavioral treatment); pain intensity score of 6 or greater out of 10 cm on the visual analog scale (VAS); and patient had been on a stable pain medication regimen for at least 28 days or was not taking pain medications as of the baseline study assessment. Key exclusion criteria were neuropathic pain due to post-herpetic neuropathy, human immunodeficiency virus (HIV), trigeminal neuralgia, or carpal tunnel syndrome; pain categorized as central (eg, spinal cord injury) versus peripheral; active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain; inability to comply with the intervention or evaluation of treatment outcomes; or a current diagnosis of progressive neurological disease such as multiple sclerosis; rapidly progressive arachnoiditis, brain or spinal cord tumor, or severe/critical spinal stenosis;

Randomization and Blinding

After completion of the baseline assessments, subjects were randomized in a 1:1 ratio to receive Magnetic Peripheral Nerve Stimulation (mPNS) along with their Conventional Medical Management (AT+CMM) or CMM alone. Due to practical considerations (see Limitations section), study subjects and investigators were not blinded to the assigned treatment group.

Interventions

Consistent with the study protocol, subjects first underwent a 7-day assessment period to measure pain scores, followed by a baseline clinical evaluation for those who met study inclusion criteria. Subjects with a score of 6 or greater on the visual analog scale (VAS) were randomized into the treatment (mPNS + CMM) or control (CMM) group.

Analgesics were stabilized from 28 days before enrollment and usage was monitored throughout the study. Adjustments were allowed under the guidance of a study investigator as medically necessary.

At 90 days, subjects from CMM were offered the option to crossover to the treatment group. The study continues to follow these patients out to 1 year.

Nerve Stimulation Procedure

In this study, subjects in the treatment group were to receive three treatments during the first week, with weekly treatments during the remainder of the month. Biweekly treatments were provided over the next 60 days, and then as needed during the remainder of the study. Each Axon Therapy procedure lasts approximately 15–20 minutes. During each treatment, patient information is entered into the system, including pre-therapy pain score and therapy location. A "Localization" procedure is performed to refine the exact therapy location and stimulus amplitude, based on patient paresthesia feedback. Those feedback stimuli responses vary, but the pulse width was always fixed at 290 microseconds and the rate pulses delivered at 0.5 hz. Once paresthesia is achieved to full length of the nerve, therapy is initiated.

Then, a preset protocol of pulses is delivered at the therapy site, while the Operator maintains proper coil position, and possibly modifies the stimulus amplitude, based on patient feedback. Post-therapy pain score is then recorded.

Initial Sample Size Calculation

It is assumed that the proportion of responders will be at least 50% (mPNS + CMM) and the proportion of responders in CMM may be 10%. The estimated responder rate in the test group (>50%) was derived from a previous pilot study.[8]

To have at least 95% power to determine that for mPNS + CMM is superior to CMM at a one-sided significance level of 0.05, a minimum of 28 subjects per group were required. To conservatively account for potential post-randomization subject loss, a total of ~60 subjects (~30 per group) will be randomized.

Randomization and Blinding

Subjects diagnosed with chronic intractable, post-traumatic and post-surgical pain will be randomized 1:1 into one of the two treatment groups:

1. CMM plus mPNS
2. CMM alone (CMM)

Subjects and clinical study staff will not be blinded to study treatment due to the nature of the difference between treatment groups.

Primary Analysis

The primary analysis for this trial was performed when the last subject completed the day 90 visit. All planned tables, listings and figures will be provided for the primary analysis for both FAS and PP populations.

A fixed sequence hierarchical testing strategy using alpha = 0.05 for between-group comparisons (CMM + mPNS compared to CMM) was applied to perform confirmatory analysis of the primary endpoint and the secondary efficacy endpoints as follows:

1. Visual Analog Scale (VAS) (in clinic) – 50% or greater without increase in baseline pain medications (primary)
2. VAS (in clinic) – change from baseline (secondary)
3. European Quality of Life 5 Dimensions 3 Level (EQ-5D-3L) – change from baseline (secondary)
4. Patient Global Impression of Change (PGIC) (secondary)
5. Brief Pain Inventory (BPI) – change from baseline (secondary)

As the primary endpoint was met with statistical significance for a one-sided test at alpha = 0.05, we proceeded to analyze the secondary endpoint results. Testing of the secondary endpoints proceeded, if applicable, utilizing a fixed sequence approach in the order specified above, using two-sided tests and alpha = 0.05. Secondary endpoints meeting statistical significance underwent subsequent post-hoc testing for subgroup differences (for example, by age, race, or gender) with Bonferroni correction. If the statistical significance was not met, hierarchical testing was not performed, and all analyses conducted on secondary endpoints then were considered exploratory. The incidence of adverse events through day 90 was also reported and compared between groups in the safety analysis set.

Results

Subject Disposition

Subjects were randomized 1:1 to CMM + mPNS or CMM only. A total of 35 subjects received CMM + mPNS and 30 received CMM. ITT included 65 subjects, while PP included 53 subjects. Ten subjects (4 in CMM + mPNS and 6 in CMM) withdrew prior to the end of study; one subject in CMM was lost to follow-up; one subject in CMM violated protocol with use of forbidden concomitant therapy. Baseline demographic characteristics (Table 1) and surgical histories were similar between CMM + mPNS and CMM for PP.

In PP, a total of 22 subjects (71.0%) in CMM + mPNS and 3 subjects (13.0%) in CMM were responders (>50% pain relief; $p < 0.0001$) (Figure 1). In PP, the mean change from baseline in VAS pain score at Day 30 was −2.97 (SD: 2.82) in CMM + mPNS compared to −0.20 (SD: 1.99) in CMM; p-value 0.0002. At Day 90, the mean change from baseline in VAS pain score was −3.76 (SD: 2.16) in CMM + mPNS compared to −0.70 (SD: 2.16) in CMM group; p-value <0.0001 (Figure 1).

In the PP set, the mean change from baseline in EQ-5D-3L at Day 90 was 0.13 (SD: 0.19) among CMM + mPNS compared to −0.06 (SD: 0.23) in CMM; two-sided p-value 0.0024. The CMM + mPNS population has 50% responders and 40% profound responders for EQ-5D-3L (Figure 2).

Table 1 Summary of Demographics, PP Population

	CMM + Axon Therapy (N = 31)	CMM Alone (N = 23)	p-value
Age (years)			
Mean (SD)	58.2 (10.8)	61.5 (13.0)	0.3335
Median (Range)	60.1 (35.1, 75.5)	67.7 (29.5, 74.0)	
Sex, n (%)			
Male	10 (32.3%)	11 (47.8%)	0.2729
Female	21 (67.7%)	12 (52.2%)	
BMI (kg/m^2)	31 31.5 (7.4) 30.4 (17.0, 44.9)	23 31.0 (6.2) 31.0 (21.6, 41.5)	

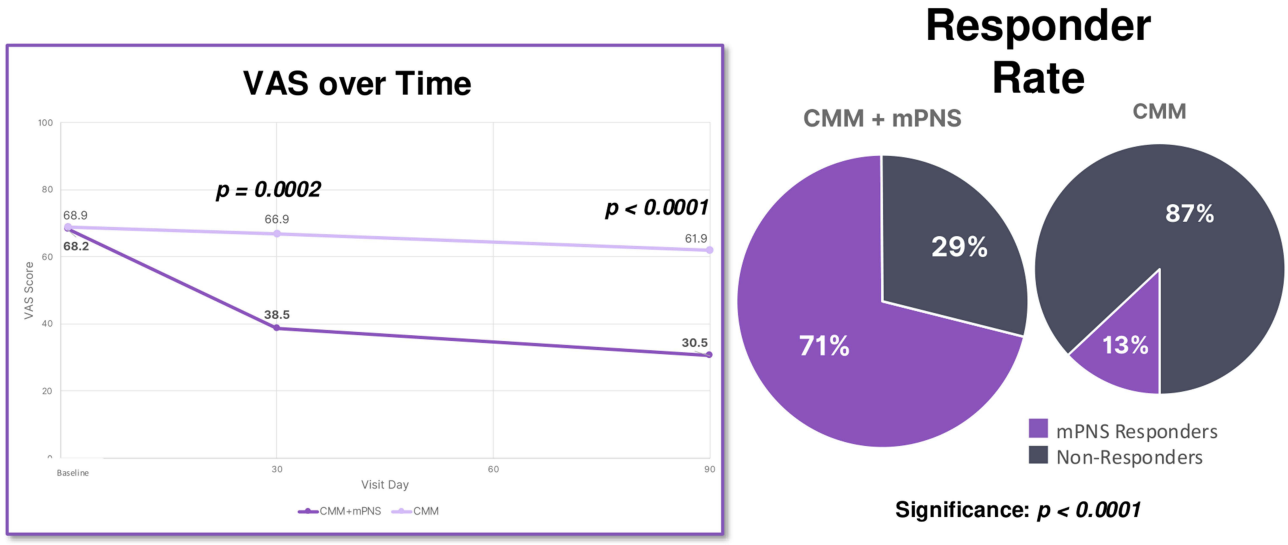

Figure 1 VAS Pain Scores at 90 days and Responder Rates mPNS+CMM & CMM.

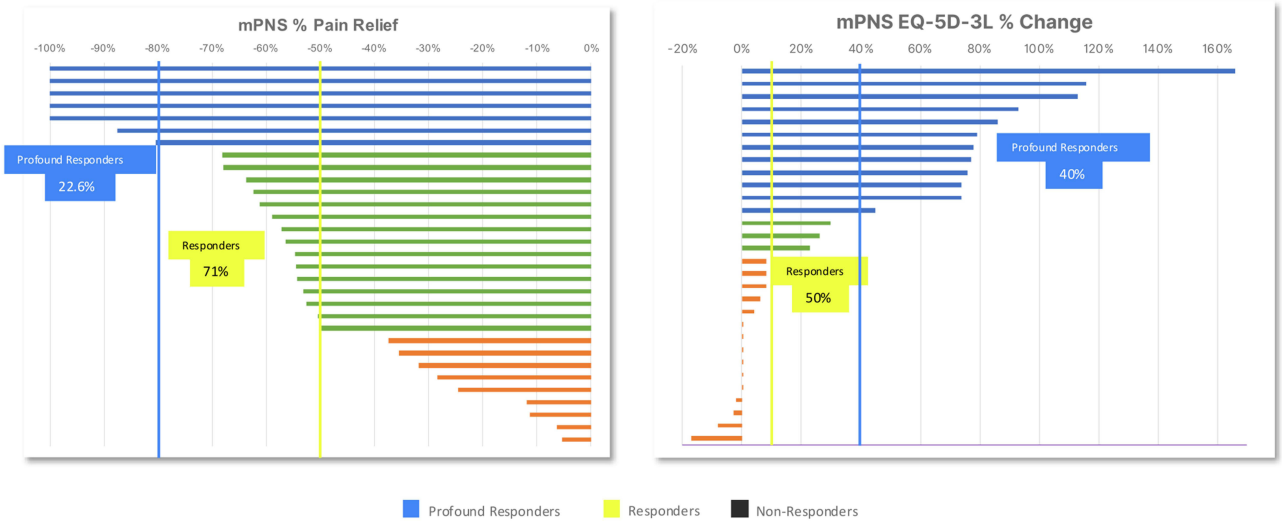

Figure 2 SEAT Study 90 day follow up VAS pain and EQ-5D-3L.

In PP, 25 CMM + mPNS subjects (80.6%) reported improvement on the PGIC compared to 1 (4.3%) CMM subject ($p < 0.0001$). Satisfaction with mPNS was reported by 83.9% (n = 26) subjects and 8.7% (n = 2) CMM subjects. The mean change from baseline in BPI at Day 90 was −2.12 (SD: 1.97) among CMM + mPNS compared to −0.33 (SD: 1.28) in CMM; two-sided p-value 0.0005 (Table 2).

Table 2 BPI Change from Baseline at Day 90, PP Population

Brief Pain Inventory	CMM + Axon Therapy (N = 31)	CMM Alone (N = 23)	Difference of mean change since baseline (95% CI)	p-value
	n Mean change since Baseline (SD)	n Mean change since Baseline (SD)		
Day 90	30 –2.12 (1.97)	22 –0.33 (1.28)	−1.80 (−2.76, −0.83)	0.0005

Table 3 Incidence of Serious Adverse Events Through Day 90, SAE Population

System Organ Class Preferred Term	CMM + Axon Therapy (N = 35)	CMM Alone (N = 30)
	n (%)	n (%)
Subjects with any SAE, n (%)	**0 (0.0%)**	**1 (3.3%)**
Infections And Infestations	0 (0.0%)	1 (3.3%)
Death	0 (0.0%)	1 (3.3%)

Abbreviations: SAE, Serious Adverse Events; CMM, Conventional Medical Management.

Safety Results

Adverse events (AE) were reported by 6 subjects (17.1%) in CMM+AT and 4 subjects (13.3%) in CMM. No AEs leading to withdrawal and no adverse device effects were reported in either group. One serious adverse event was reported in the CMM group. One death was reported in the CMM group. Two subjects (5.7%) with treatment-related AEs were reported in CMM+AT (1 subject with ankle pain, 1 subject with shoulder pain) all unrelated to AT procedure (Table 3).

Discussion

Efficacy

The SEAT Study is first multi-center, randomized controlled trial demonstrating the superiority of mPNS and CMM versus CMM alone. Pain responder rate in this study was a significantly higher in mPNS plus CMM group when compared to CMM study group. In addition, changes in functional capacity and patient satisfaction, as measured by EQ-5D-3L and PGIC, suggested a great benefits to subjects who used mPNS in completing activities of daily living and improved mobility.

The NNT (>50% of pain relief) of mPNS, as shown here, is 1.4. Such result was previously documented in studies when invasive therapeutic modalities were used to treat neuropathic pain, like implanted PNS and SCS systems. Since mPNS is a completely non-invasive procedure, it may improve patient access to neuromodulation at a significantly lower risk and cost.

Furthermore, and as shown in this study, outcomes of mPNS are superior to outcomes of the most commonly used membrane stabilizers, like gabapentin and pregabalin, for neuropathic pain. NNT of gabapentin and pregabalin exceed 7[7] while as suggested above mPNS NNT is 1.4. Based on immediate effect of mPNS therapy without inherited medication side-effects, we may need to rethink current algorithm for treatment of various types of mononeuropathies and peripheral neuropathies, like the one in diabetes. Early usage of mPNS may eliminate and/or minimize usage of commonly prescribed membrane stabilizers, antidepressants and other medications for neuropathic pain.[7] In addition, addictive nature of most prescribed neuropathic drugs, pregabalin and gabapentin came in focus recently as more reports of physical dependency to gabapentin and somewhat more to pregabalin prompted a new classification of those medications.[10]

Safety

mPNS is a generally safe and non-invasive therapy and the SEAT Study results support that conclusion. The 2 TRAE's reported were unrelated to the therapy, not in the primary treatment area and did not affect either subject for an inordinate amount of time. Both subjects completed the Study as well.

The results of the SEAT Study are similar in terms of responder rate and absolute pain reduction to the retrospective analysis of mPNS by Bedder and Parker.[5] In addition, this non-invasive therapy provides responder rates similar to more invasive procedures like implanted peripheral nerve stimulators and spinal cord stimulators.[3]

Limitations

More peripheral neuropathies, like painful diabetic neuropathy, should be studied as clinical outcomes may be similar or even better than in the SEAT Study.

As previously noted, a larger sample size, while not impacting significance, would provide an additional evidence of the efficacy and safety of the therapy. In addition, as this was a study using CMM as a control, there is a possibility of placebo effect as there was no sham control. This should be addressed in future studies of mPNS. Another consideration is the interaction of pain medications with mPNS. Investigators were allowed to adjust subjects' pain medication dosing during the study. Changes to opioid analgesics have the potential to confound the effects of mPNS. However, no pain medication usage was increased in the mPNS group. Because the study was not designed to resolve the chemical or psychological issues related to chronic use of pain medications, the effect of mPNS on chronic opioid use requires further study. Also further assessment of cost-effectiveness of such intermittent therapy when compared with early treatments for neuropathic pain needs to be addressed in upcoming studies.

Conclusion

Improvements in pain relief and quality-of-life after using mPNS therapy were significant and profound in SEAT Study. This suggests that mPNS should be considered very early in the chronic pain treatment algorithm before any invasive procedure.

Site Information

Center for Clinical Research, Winston Salem, NC.

IPM Medical Group, Walnut Creek, CA.

Crescent Moon Research, Murrell's Inlet, SC.

National Spine and Pain, Shrewsbury, NJ.

Data Sharing Statement

The authors of this study do not intend to share the individual deidentified participant data. The risk regarding privacy is significant and of concern to authors. Study documents and clinical study reports will be shared through clinicaltrials.gov per their guidelines and access rules.

Acknowledgments

Joe Milkovits, COO NeuraLace Medical for technical support in the production of this manuscript, JoAnn Kuhne, Kara & Associates for Clinical Trial Management, Heidi Reichert, Toxstrategies for Statistical Analysis, Danielle Cox for management of Trial Operations.

Funding

Neuralace Medical.

Disclosure

LK serves on advisory boards for Biotronik, Gimer, Neuralace, PainTEQ, and Presidio and has research agreements with Neuros, Nevro, FUS Mobile, Saluda, and Nalu.

KA is a consultant for Nevro, Saluda, Biotronik, Boston Scientific, and Presidio.

JR is a consultant for Neuralace Medical.

Dr. Li serves as a consultant for Abbott, Avanos, Averitas Pharm, Biotronik, Boston Scientific, Nalu Medical, Nevro, PainTEQ, Saluda Medical, SPR Therapeutics, Vertos Medical, and is on the Speaker's Bureau for Scilex Pharm, and has Stock Options in Nalu Medical. He has received research support from Avanos, Biotronik, Boston Scientific, SGX Medical, Nalu Medical, PainTEQ, Saluda Medical, and SPR Therapeutics.

MB is a consultant for Neuralace Medical and Boston Scientific. He Chairs the Advisory Board for Neuralace Medical.

The authors report no other conflicts of interest in this work.

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