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Spinal Cord Stimulation: Comparing Traditional Low-frequency Tonic Waveforms to Novel High Frequency and Burst Stimulation for the Treatment of Chronic Low Back Pain

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Abstract

Purpose of Review The purpose of the present investigation is to summarize supporting evidence for novel sub-perception spinal cord stimulation (SCS) therapy over traditional paresthesia inducing low-frequency waveforms for the treatment of chronic pain. The focus of this review is to summarize key studies comparing traditional low-frequency tonic waveforms to modern high frequency and burst stimulation for the treatment of patients with chronic intractable low back pain and/or leg pain.

Recent Findings Several recent studies have demonstrated the benefit of novel SCS therapies over traditional low-frequency SCS for the treatment of patients with chronic low back and/or leg pain. SENZA-RTC showed that paresthesia-free high-frequency SCS was superior to low-frequency stimulation for treatment of chronic low back pain with leg pain. The SUNBURST crossover trial recently found that high-frequency burst stimulation was preferred over low-frequency tonic SCS with patients citing better pain relief and a preference for paresthesia-free SCS. The new ongoing EVOLVE workflow retrospective multicenter study uses technology that can deliver both low-dose and high-dose SCS. Further, the wavewriter technology addresses patient variability with its ability to layer sub-perception waveforms and paresthesia inducing low-frequency stimulation tailored to patient needs via an interactive feedback feature.

Summary Neuromodulation for the treatment of chronic pain is rapidly evolving with technology at its forefront. Modern SCS systems use novel waveforms, frequencies, and stimulation modes to deliver paresthesia-free pain relief to patients suffering from chronic low back pain and/or leg pain with better results than traditional tonic low-frequency SCS. As the field advances, new studies are needed comparing new waveform and delivery systems to optimize patient selection and treatment response.

Keywords Waveform · Spinal cord stimulator · Back pain · Frequency · Outcomes

Introduction

An estimated 100 million Americans suffer from chronic pain. Low back pain has the highest prevalence, affecting approximately 8–11% of the population [1, 2]. Chronic pain typically affects many aspects of a person's life. It can cause emotional distress and/or psychosocial impairment [3] and is the number 1 cause of disability in adults in the USA [4]. Unfortunately, current treatment options have shown limited effectiveness for the treatment of chronic pain [4]. More recent studies have shown that opioid analgesics may be clinically inappropriate for the long-term treatment of chronic pain and pose the risk of addiction [5, 6]. Neuromodulation, first introduced in 1967 by Shealy et al. [7], has been approved as a treatment option for various chronic intractable pain syndromes in an effort to better serve chronic pain patients. Early on in its development, innovations in hardware focused primarily on size reduction and MRI compatibility. More recently, there has been a paradigm shift from hardware to software innovation to improve effectiveness and patient tolerability. The traditional SCS system focuses on paresthesia-inducing stimulation that overlaps pain distribution with the intent of masking pain perception. These SCS systems typically use lower frequencies in the range of

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40–60 Hz and require intraoperative mapping by soliciting patient feedback to adjust stimulation location, pulse frequency, width, and amplitude. This mode of neuromodulation relies on the adequacy and durability of paresthesia coverage as well as patient tolerance to achieve effectiveness. In the treatment of chronic axial back and limb pain, adequate paresthesia coverage in the back region has shown to be more challenging, making traditional SCS delivery systems better for treatment predominantly of leg pain [8–10]. More recently, there has been a paradigm shift toward paresthesia-free high-frequency stimulation. This novel type of neuromodulation focuses on high-frequency (1–10 kHz), low-amplitude (1 to 5 mA) pulses which potentially obviates the need for intraoperative mapping and has shown the ability to treat chronic low back pain with increased durability [11, 12]. In response, SCS manufacturers have devised randomized controlled clinical trials comparing traditional low-frequency paresthesia producing stimulation to novel high-frequency neuromodulation for the treatment of low back with with/without leg pain. In this article, we discuss some of the pivotal trials at the forefront of this new paradigm in neuromodulation for the treatment of chronic pain of the lower back and legs.

SENZA-RCT Randomized Controlled Trial

Study Purpose

The Nevro corporation devised a multicenter, randomized, controlled, pivotal trial comparing the safety and efficacy of high-frequency 10 kHz (HF10) therapy to traditional SCS in patients with chronic intractable back and leg pain [13••]. As a result of this trial, HF10 subsequently gained Food and Drug Administration (FDA) approval in May 2015 following their published 12-month trial data and became the only device to receive a paresthesia-free label. Twenty-four-month data was also published in a follow-up study showing sustained superiority over traditional SCS [14••].

Patient Selection and Study Design

In this study, a total of 198 patients with both back and leg pain were randomized in a 1:1 ratio to a treatment group across 10 comprehensive pain treatment centers. Of these, 171 passed a temporary trial and were implanted with an investigational HF10 therapy system (90 patients with Senza® System; Nevro Corp., USA) or a commercially available SCS system (81 patients with Precision Plus System; Boston Scientific, USA). Key inclusion criteria were: chronic, intractable pain of the trunk and/ or limbs, refractory to conservative therapy for a minimum of 3 months (previous conservative treatments included pain medications, physical therapy, spinal injections, pharmacological, and behavioral treatment); an average back and leg pain intensity of 5 or greater out of 10 cm on the visual analog scale (VAS); an Oswestry Disability Index (ODI) version 2.1a score of 41 to 80 out of 100; the patient was an appropriate candidate for the surgical procedures required in this study. Key exclusion criteria for the study included active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain, inability to comply with the intervention or evaluate treatment outcomes, mechanical spine instability based on flexion/ extension films of lumbar spine, or prior experience with SCS. The primary endpoint of the study was a composite of safety and efficacy: the percentage of subjects who respond to SCS therapy for back pain (≥ 50% reduction in VAS score) without a stimulation-related neurological deficit. In addition to classifying the subjects as responders or non-responders, subjects were classified remitters or non-remitters (pain remitter defined as having a VAS pain score of 2.5 or less). The primary efficacy assessment occurred at 3 months post device activation and follow-up continued through 12 months for the initial US publication. A follow-up article later presented secondary results at 24 months. Secondary endpoints included percentage changes from baseline in back pain, leg pain, and ODI. Non-inferiority was first assessed, and if demonstrated, the results were tested for superiority. The main results are summarized below.

Results at 3 Months

At the initial 3-month follow-up, 84.3% of implanted HF10 therapy subjects were responders for back pain versus 43.8% for traditional SCS [RR 1.9 (1.4–2.5) CI 95%]. HF10 leg pain responders were 83.1% versus 55% for traditional SCS [RR 2.1 (1.4–3.0) CI 95%]. HF10 therapy had 65.2% remission for back pain versus 31.3% for traditional SCS [RR 2.1 (1.4–3.1) CI 95%]. Leg pain remission for HF10 was 76.4% versus 37.5% for traditional SCS [RR 2.0 (1.5–2.8) CI 95%].

Results at 12-Months

Back pain responder rate was approximately 80% for HF10 therapy compared with approximately 50% for traditional SCS. Leg pain responder rates show a similar advantage for HF10 therapy. Notably, approximately 67% of subjects receiving HF10 therapy were back and leg pain remitters over the 12-month follow-up period versus approximately 35% remitter for back pain and 40% for leg pain with traditional SCS, respectively.

Results at 24 Months

HF10 therapy showed a similar advantage in terms of responder rates, reporting 76% for back pain and 73% for leg pain for HF10 vs. 49% for both leg and back pain with traditional SCS.

Remission rates were also significantly better for HF10 (back pain: 65.9% vs 31.0 and Leg pain: 65.9% vs 39.4%).

VAS Score Results

With respect to VAS score, back pain decreased to a greater degree at 24 months for HF10 therapy subjects with reported VAS score of 2.4 for both back and leg pain (back pain point decrease: 5.0 ± 2.5 cm; leg pain point decrease: 4.7 ± 2.8 cm). Traditional SCS subjects reported VAS scores of 4.5 for back and 3.9 for leg pain, respectively. Of note, average baseline VAS scores for HF10 and traditional SCS cohorts were 7.4 (1.3) and 7.8 (1.2), respectively.

Study Limitations

Several study limitations were discussed. The potential interaction of pain medication with SCS therapy was considered, though more HF10 subjects reduced or eliminated opioid analgesics than traditional SCS subjects; thus, opioid analgesics were likely not responsible for the superior effectiveness of HF10 therapy. Investigators and subjects were not masked to the assigned treatment groups since low-frequency SCS produces paresthesias; future studies with paresthesia-free SCS trial periods will remedy this problem. Subject heterogeneity in pain diagnoses was also considered (though 75–80% had FBSS) and authors mentioned the clinical relevance of this heterogeneity as representative of the diversity of patients seen by pain specialists. Lastly, this was an industry-sponsored study and funded by Nevro Corp., Menlo Park, California. Overall, this study confirms the superiority of high-frequency neuromodulation. It gained the superiority label of approval from the FDA for HF10 over traditional SCS treatment.

The SUNBURST Randomized Controlled Trial

Study Purpose

This was a multicenter, randomized, unblinded, crossover trial aimed to determine the safety and efficacy of a device delivering both traditional tonic stimulation and high-frequency burst stimulation to patients with chronic pain of the trunk and/or limbs. Non-inferiority measures for burst and ultimately superiority were to be established. Furthermore, this study was designed to provide evidence to support US FDA approval of the burst spinal cord stimulation mode as a treatment for chronic intractable pain, using a single device which allows patients to use both tonic and burst stimulation (US FDA approval October 4, 2016).

Background

Burst stimulation consists of groups of higher-frequency pulsed stimulatory (charge) phases, separated by pulse-free interphase delays, ultimately followed by a passive recharge (discharge) phase. This is thought to allow for full recovery of any briefly accumulated charge during the stimulatory or charge phase. The burst waveform potentially emulates naturally occurring neuronal firing modes in the central nervous system [15]. Several early studies have suggested that burst stimulation provides better pain relief than tonic stimulation. [16–20] In response to these findings, this larger controlled study was developed to demonstrate not only superiority to tonic stimulation but also the safety and efficacy of burst stimulation as well as to gain United States Food and Drug Administration (FDA) approval for the treatment of chronic trunk and/or limb pain [21••]. This study was designed as a 24-week cross-over trial during which subjects used one stimulation mode for 12 weeks and then crossed over to the other for the remaining 12 weeks, followed by an open-label phase during which study participants could use either waveform.

Patient Selection and Study Design

A total of 121 subjects underwent an evaluation using an SCS trial system with tonic stimulation. Ultimately, 100 subjects received a permanent implant and were randomized to either treatment arm 1 (tonic first/burst second, $n = 45$) or treatment arm 2 (burst first/tonic second, $n = 55$). Subjects with chronic intractable pain of the trunk and/or limbs with a baseline average daily overall pain score of ≥ 60 on the VAS collected with a 7-day Pain Diary were included in the study. Subjects with a history of a neurostimulation trial or implant system, an overall Beck Depression Inventory II score > 24, or who had already participated in a clinical trial with an active treatment arm were excluded from the study. Participants who achieved adequate pain relief during a traditional tonic trial evaluation (at least 50% improvement in patient-reported pain) were implanted with a rechargeable neurostimulation system (ProdigyTM, Abbott, Plano, TX, USA) that can deliver both tonic and burst stimulation. Subjects were randomly assigned 1:1 to either receive tonic (programmed pulse width ranged between 100 and 500 msec with frequencies typically between 30 and 100 Hz and amplitude producing comfortable paresthesias per patient's perception) or burst stimulation (500 Hz delivered in groups of five pulses with a 1 msec pulse width, with the five pulses repeated at a frequency of 40 Hz; target amplitude was tailored to patient comfort level) for first 12 weeks and would then cross over to opposite study arm for additional 12 weeks. Patients were assessed at 6, 12, 18, 24 weeks following randomization, then every 6 months for 2 years during the open-label phase of the study after the initial 24 weeks. Assessments included 7-day Pain Diaries prior to

each study visit, SF-36v2TM Health Survey for quality of life assessment, the pain catastrophizing scale (PCS) to assess the quality of thoughts and feelings during pain, the Oswestry Disability Index 2.1a (ODI) to assess a person's functional level, and paresthesia mapping. The primary endpoint of study was to establish noninferiority of burst compared to tonic stimulation. If this goal was met, secondary endpoints were analyzed in a step-down process, where testing only continued if significant results were achieved. At the first nonsignificant result, all testing would stop. Secondary endpoint #1 would determining what proportion of participants achieved 30% or greater change from baseline in overall VAS score. Secondary endpoint #2 was an analysis of the presence of paresthesia to demonstrate the differences between the two stimulation modes. Finally, statistical analysis (two-sample *t* test) was used to demonstrate that the change in VAS score with burst stimulation is superior to that using tonic stimulation. The results are summarized below.

Study Results

The overall VAS score difference between burst and tonic stimulation was − 0.51 cm, with a mean difference between burst and tonic stimulation of − 0.114 cm, meeting the primary endpoint of the study (non-inferiority margin). In addition to noninferiority, statistical superiority of burst stimulation over tonic stimulation in overall VAS ($p < 0.017$), trunk VAS ($p < 0.013$), and limb VAS ($p < 0.045$) was also achieved. Individual analysis of both trunk and limb VAS score was assessed after 12 weeks of each stimulation mode. Trunk VAS scores following burst stimulation were 0.57 cm lower than scores following tonic stimulation. Similar results were seen with limb pain, with lower VAS scores following burst stimulation than VAS scores following tonic stimulation.

VAS Scores

Clinically significant reductions in VAS (or responder rates) were defined by the study protocol as a decrease from overall daily VAS score from baseline by at least 30%. A total of 69/100 subjects (69.0%) responded to tonic stimulation, burst stimulation, or both; while 60.0% (60/100) of subjects were responders to burst stimulation and 51.0% (51/100) of subjects were responders to tonic stimulation.

Paresthesia Mapping

Paresthesia mapping at both 12 and 24 weeks was available for 73 subjects. A total of 61.6% were paresthesia-free using burst stimulation while only two subjects (2.7%) were paresthesia-free using tonic stimulation. A total of 27.4% of subjects reported some reduction (> 1% or < 100% reduction) in paresthesia sensations on the body map during burst stimulation as compared to tonic stimulation.

Subject Satisfaction Analysis

Subject satisfaction and stimulation preference were also assessed during the study. Significantly more subjects preferred burst stimulation over tonic stimulation (70.8% vs. 18.8%), while 10 subjects (10.4%) had no preference between the two stimulation modes. Subjects were asked the reason for their stimulation preference. Of the subjects who chose burst over tonic stimulation, 47.1% cited "lack of paresthesia" as the primary reason for their preference, while 45.6% cited "better pain relief" at 24-week follow-up. This trend was sustained through the 1-year follow-up and 68% of subjects used burst as their most used program type.

Psychosocial and Physical Function Assessments

Interestingly, several psychosocial and physical function assessments were examined during the course of the study. The Short Form McGill Pain Questionnaire (SF MPQ-2) was used to assess both the sensory and affective components of pain. Patient Global impression of change questionnaire [22] (higher score indicates pain experience greatly affects thoughts and feelings) and Beck Depression InventoryVR-II (BDI-II) were also assessed. The study found no significant difference between burst or tonic stimulation for these assessments. Furthermore, each subject's disability was assessed using the validated ODI [23] showing reduction in ODI scores from baseline following both stimulation modes but no statistical difference between the two.

Study Limitations

Crossover trials have an inherent limitation, which is the potential carryover effect in this type of study design. Washout periods are typically used to minimize any carryover effects; however, the study cites previously documented subject failure to comply with the study protocol when asked to undergo periods without stimulation [24]. In addition, pain relief assessments occurred at 12 weeks after changing stimulation modes, which was adequate time to ensure that any residual of the previous therapy would not influence the assessment of the current therapy as noted in previous trials [25, 26]. This study likely inherently favored the tonic group as the trial period only randomized subjects that responded to tonic stimulation. In this context, the study was also unable to assess the effectiveness of burst stimulation in subjects who had failed traditional tonic SCS. Other studies have suggested that burst stimulation may be used to salvage chronic pain patients who fail to respond, or who have over time become poor

responders to traditional tonic stimulation [17, 18]. This remains an area of future research.

In keeping with the Initiative on Methods, Measurement, and Pain Assessment on Clinical Trials (IMMPACT) [27] recommendations to include assessments of physical and emotional functioning, patient-reported improvement and satisfaction and assessments beyond VAS scores were included in this study. Subjects in this study had low baseline PCS scores (below level of clinically significant pain catastrophizing) and ODI scores (below what is typically seen for chronic pain patients) - combined with the exclusion of patients with very high BDI-II score (> 24) these factors likely caused the inability to demonstrate statistical significance between burst and tonic stimulation. Lastly, this was an industry-sponsored study by Abbott (formerly St. Jude Medical).

Ongoing Industry Sponsored Clinical Trials

Medtronic technology is also paving the way for high-frequency neuromodulation for the treatment of chronic pain syndromes. The Evolve Workflow trial is a retrospective, multicenter (four US sites) cohort study evaluating novel high-dose SCS Workflow for post-laminectomy back and leg pain using the Medtronic RestoreSensor spinal cord stimulation software [28]. The study protocol uses high-dose (HD) stimulation (pre-defined with 1000 Hz, 90 μs) before low-dose (LD) stimulation. Key inclusion criteria include post-laminectomy or chronic postoperative pain, patients diagnosed with low back and/or chronic leg pain, documented trial that began with HD stimulation at or around the T9–10 interspace. Preliminary results from this study recently presented at the American Society of Regional Anesthesia and Pain Medicine meeting in 2017 are promising and support prior data that high-dose neuromodulation is more effective and better tolerated than traditional SCS. Sixty-nine percent of patients ($N = 87$) were responders (≥ 50% change in pain score) with a reported 76% improvement in pain scores for responder group at 3-month assessment. A total of 18 patients completed 3+ month follow-up visit and reported sustained pain relief (average initial pain score 7.47 versus 3+ month average pain score 2.44). Of note, 89% (16/18) of patients that completed the 3+ month follow-up were preferentially using HD over LD. A total of 5.6% were using low dose and 5.6% were using a combination of the two stimulation modes, respectively.

Early in 2018, Boston Scientific Corporation announced FDA approval for its new Spectra WaveWriter™ Spinal Cord Stimulator (SCS) System. This is the first and only system approved by the FDA to simultaneously provide paresthesia-based and sub-perception therapy. Boston Scientific gained FDA approval by citing previously published clinical trials to support the safety and effectiveness of the Spectra Wavewriter, with the premise that this new system is similar to the SCS systems already studied (with respects to intended use, target patient population, technology, device design, and output characteristics). By layering more than one therapy at the same time (HF, Burst, Tonic) and delivering multiple therapies over time, the Spectra WaveWriter hopes to provide more thorough and longer-lasting pain relief. A unique feature of this system allows patients to enter real-time evaluations via remote control in response to automatically rotating waveforms. Currently, 64 patients are enrolled in the study with a primary outcome measure of 50% or greater reduction in overall pain from baseline. Indications for the Spectra Wavewriter currently include chronic pain of trunk and/or limbs associated with failed back surgery syndrome, complex regional pain syndrome (CRPS) types I and II, intractable low back pain and leg pain. The estimated study completion date is late 2021.

Discussion

The previous decades of innovation in neuromodulation have focused on hardware with smaller batteries, more electrodes, accelerometers, and wireless capabilities. Nevro's introduction of HF10 therapy sparked a paradigm shift with every company investing in software innovation to achieve superior efficacy for patients suffering from chronic pain. Neuromodulation is one of the most rapidly innovating segments of biotechnology with efforts focused on expanding indications for neuromodulation, finding the optimal waveforms, and continued hardware improvement.

At present, neuromodulation has a broad breadth of applications for the treatment of chronic pain (i.e., FBSS, limb ischemia and related pain states, angina pectoris). As the industry advances, subthreshold SCS systems have shown superiority over traditional tonic stimulation and improved adoption by the large majority of patients. The superior efficacy with low-risk profile of subthreshold SCS as compared to alternative treatments has a favorable appeal in terms of healthcare economic benefits. Considering the opioid crisis facing the USA, expanding the indications of neuromodulation and demonstrating durable efficacy will dramatically improve patient care while decreasing overall healthcare utilization. While strong evidence to support the effectiveness of neuromodulation in helping to wean patients off opioids while treating their pain syndrome is lacking, there is a trend in recent data to suggest this potential benefit (i.e., over one third of subjects receiving HF10 therapy reduced or eliminated their opioid analgesic intake in the SENZA trial, despite an average of 13 years of chronic pain). In the context of the opioid addiction epidemic and insufficient evidence to support the use of long-term opioid analgesics for the management of chronic pain,

neuromodulation offers the promise to make a significant impact on this very complex problem.

Continued research in neuromodulation is imperative with attention directed toward mechanism of action and finding the optimal waveforms tailored to individual patients. A major limitation for high-quality studies is the immense cost of large, controlled trials. Published and future studies require industry sponsorship leading to inherent bias; however, it appears that all the neuromodulation companies are committed to pushing the entire field forward.

Conclusion

Spinal cord stimulation is a major tool in the armamentarium of pain physicians to treat chronic pain and reduce opioid consumption. Physicians and patients now have multiple options of vendors and waveforms. In this investigation, current studies were reviewed supporting different waveforms and settings in neuromodulation.

Compliance with Ethical Standards

Conflict of Interest Ariel Morales declares no conflict of interest. R. Jason Yong, MD MBA serves as a consultant for Nevro and Medtronic. Alan D. Kaye, MD PhD serves on the Speakers Bureau of Depomed and Merck. Richard D. Urman MD MBA received research funding from Medtronic, Merck, Mallinckrodt and an honorarium from 3M and Sandoz.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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