



Burst Spinal Cord Stimulation in the Management of Chronic Pain: Current Perspectives

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Abstract

Over the last several decades, opioid diversion, misuse, and over-prescription have run rampant in the United States. Spinal cord stimulation (SCS) has been FDA approved for treatment for a primary indication of neuropathic limb pain that is resistant to more conservative medical therapy. The disorders qualified for treatment include neuropathic, post-surgical, post-amputation, osteodegenerative, and pain related to vascular disease. Some of the most frequently cited conditions for treatment of SCS include failed back surgery syndrome, complex regional pain syndrome (CRPS) Type I and Type II, and post-herpetic neuralgias. Developments in SCS systems have led to the differentiation between the delivered electromechanical waveform patterns, including tonic, burst, and high-frequency. Burst SCS mitigates traditional paresthesia due to expedited action potential and offers improved pain relief. Burst SCS has been shown in available studies to be non-inferior to the traditional SCS, which can cause pain paresthesia in patients who already have chronic pain. Burst SCS does not seem to cause or need the paresthesia seen in traditional SCS, making SCS not tolerable to patients. Moreover, some studies suggest that burst SCS may decrease opioid consumption in patients with chronic pain. This can make burst SCS an extremely useful tool in the battle against chronic pain and the raging opioid epidemic. As of now, more research needs to be performed to further delineate the effectiveness and long-term safety of this device.

Keywords: Spinal Cord Stimulation, Chronic Pain Management, Burst Stimulation, Failed Back Surgery Syndrome, Neuropathic Pain, Complex Regional Pain Syndrome

1. Context

Spinal cord stimulation (SCS) has been FDA approved for treatment for an essential indication of neuropathic extremity pain that is resistant to more conservative medical therapy (1). Additional benefits of SCS therapy include reduced narcotic use, improved quality of life, and more opportunity of coming back to their work-life (2). The disorders qualified for treatment include neuropathic, post-surgical, post-amputation, osteodegenerative, and pain related to vascular disease (1, 2). Some of the most frequently cited conditions for treatment of SCS include failed back surgery syndrome, complex regional pain syndrome (CRPS), and post-herpetic neuralgias. CRPS is a painful neuropathic condition affecting the distal aspect of a limb that may or may not be precipitated through in-

jury. Currently, CRPS is categorized into Type I, characterized by an initiating injury or cause of immobilization, and Type II demonstrated through a known nerve injury (3).

Although CRPS can be difficult to treat, several clinical studies have reported high success rates of pain relief with SCS in trial insertion and long-term therapy (3, 4). Furthermore, a recent case report demonstrated thermographic findings in the treatment of Type II CRPS through SCS and clinical reports of 60 - 80% of patients experiencing pain relief for CRPS Type I (2, 4). Physical evidence of edema, sweat gland abnormalities, or abnormal blood flow to the affected site may be present. Although the pathophysiologic mechanism is not well understood, tissue inflammation, vasomotor dysfunction, central neurologic sensitization, and neuroplasticity are believed to be involved (5).

SCS targets hyperexcitable central neural pathways and efferent sympathetic transmission related to CRPS pain signaling (6). Despite these successes, some CRPS patients do not experience adequate relief, or pain control diminishes over time (5). Current studies also suggest that post-herpetic neuralgia can be managed through SCS therapy. PHN produces painful paresthesia along the dermatomal pattern affected by the Herpes Simplex virus, showing persistent resistance to analgesic pharmacotherapy (6).

Chronic pain related to degenerative spinal disorders and post-back surgery can often remain refractory to conservative measures and require prolonged courses of narcotic medical management (7). Furthermore, one source reported that 15-40% of patients would experience chronic back and limb pain after lumbar surgery (6). Many of these conditions are suggested to be treated through SCS, including failed back surgery syndrome, post-laminectomy pain, multiple back operations, peripheral causalgia, epidural fibrosis, and arachnoiditis. Vascular etiologies have also been suggested for therapy with SCS, and both inoperable peripheral vascular and inoperable angina-related pain have shown improved pain relief, quality of life, and limb mobility (2). While many of these painful, difficult to treat conditions, SCS has provided adequate therapy in cases refractory to conservative management and may lead to prolonged pain relief, decreased narcotic requirement, and improved quality of life (3).

2. History of Spinal Cord Stimulation

The first demonstration of electrical neurostimulation of the spinal cord to treat chronic pain in 1967 began an era of a new approach to treat chronic pain that would continue to grow throughout the last 50 years. Only two years before the first spinal cord stimulator, in 1965, Melzack and Wall published their proposed "Gate Control" theory of the electrical influence of neurochemical transmission through GABAergic pathways (8). Since its early development, the progression of device features provides further improvements, a minimally invasive approach, variations in electromechanical waveforms, and an increased number of electrodes from 8 to 16 (1). During the 1970s and 1980s, SCS became an accepted method for treating neuropathic and ischemic pain states (9). One study conducted in 2005 approximated that in 1998 there were 5,000 patients in Europe and 15,000 worldwide with implanted spinal cord stimulators (6). Furthermore, by 2018 an estimated 50,000 SCS systems are implanted annually and will continue to demonstrate an increased demand as SCS trial numbers among the Medicare population showed a 12.4% annual increase and a 186% total increase from 2009 to

2018 (10). SCS has also played a pivotal role in reducing narcotic use in chronic pain and has shown clinical evidence for treatment of several chronic pain-related states, including failed back surgery syndrome, complex regional pain syndrome, post-herpetic neuralgia, amongst other neuropathic and vascular-related pain disorders (10).

Developments in SCS systems have led to the differentiation between the delivered electromechanical waveform patterns, including tonic, burst, and high-frequency (11, 12). Conventional SCS therapy delivered electrical currents through tonic stimulation at a low frequency (LF) (40 - 60 Hz), low amplitudes up to 5 mA, and a shorter pulse width of 30 microseconds, eliciting comfortable paresthesia to painful foci. This stimulation activates the dorsal columns of the spinal cord through the lateral discriminatory pathways and large-diameter alpha and beta sensory afferents nerve fibers (13). Paraesthesia-based mapping during lead placement allows the provider to ensure adequate dermatomal coverage to painful foci (8, 14). More recently, 10-kHz high-frequency (HF), and burst, SCS utilizes different frequencies and intensities than tonic stimulation, avoiding intraoperative paresthesia mapping and undesirable paresthesia altogether during therapy. These newer developments allow for improved pain scores and provide patients with a more comfortable and enhanced experience (15).

During the past decade, clinical evidence has emerged for both of these newer variations of SCS has shown improved outcomes and overall efficacy compared with traditional tonic SCS. A recent multicenter randomized controlled trial (RTC) demonstrated non-inferiority and long-term superiority to treating chronic back and leg pain with HF 10-kHz compared to traditional LF SCS. As of May 2015, the FDA has approved paresthesia-free therapy with HF 10-kHz therapy for these conditions (16).

In addition to HF 10-kHz stimulation, clinical evidence published in 2010 and 2013, introduced by DeRidder and colleagues, provided a new clinically proven approach to SCS through burst stimulation. Initial designs of burst stimulation represented stimulatory patterns measured in the thalamus. Currently, designs operate by producing intermittent electrical pulses at 500 Hz up to 40 times per second (9, 15). The SUNBURST trial in 2017, the largest prospective, multicenter RCT comparing burst SCS with control LF-SCS, further demonstrated greater pain relief associated with settings of lower amplitude provided by burst as opposed to tonic stimulation. This study was designed as a non-inferiority crossover trial performed under strict FDA guidelines and initially conducted for gaining FDA approval (15).

Although SCS has shown safe implementations due to its minimally invasive nature and reversible features,

reports of harmful effects arise from procedural complications or hardware malfunction (17). Procedural complications include infection, epidural abscess, epidural hematoma, post-dural puncture headache, and potentially paralysis. Recent studies have shown infection to be the most frequent procedural complication and lead migration to be the most frequent technical complication (3, 18). While various complications can arise, proper candidate selection and medical optimization are suggested to allow for greater improvements in pain in a safe, effective manner.

3. Technological Improvements in Spinal Cord Stimulation

Spinal cord stimulation was first used in 1967 (1). Conventional therapy in SCS used moderate frequency electrical stimulation to create paresthesia over painful areas (1). Over the last decade, there have been many advances involving lead design, stimulator features, and waveform paradigms (1). Traditionally, SCS used short-duration pulses with frequency ranges of 40 - 60 Hz (19). However, thalamic neuronal firing corresponds to a higher number and frequency of action potentials (1). Burst SCS is a novel approach developed to address the issue by delivering intermittent bursts of electric pulses at high frequency (5 pulses at 500 Hz delivered 40 times/second) (20). Burst SCS mitigates traditional paresthesia due to expedited action potential and offers improved pain relief (20). Cessation of traditional paresthesia improves function and quality of life (21). Furthermore, Burst SCS was approved in 2016, and research has shown that burst SCS relies on different mechanisms than traditional SCS modulating ascending and descending pain pathways (22).

In addition, to burst SCS, kilohertz-frequency SCS (KHFSCS) is a novel approach to SCS (1). KHFSCS applies tonic stimulation at > 1 kHz (16). The high frequency of KHFSCS translated to paresthesia cessation. KHFSCS propagates the idea of the conduction block (22). Conduction block is a term describing the inhibition of a propagating nerve impulse. However, when used clinically, KHFSCS's low stimulation amplitude is unlikely to produce a significant conduction block (23). De Carolis et al. proposed pain paresthesia overlap is not necessary for KHFSCS pain relief (24). Furthermore, KHFSCS proposed mechanisms of action include asynchronous activation, desynchronization, and dorsal horn cell suppression (25). Thus, KHFSCS is a novel effective approach for SCS pain relief. Lead placement innovation has been advantageous in spinal cord stimulation.

Advances in electrode placement have also occurred. Electrodes deliver neuronal stimulation to areas with over-

lapping pain and neuronal hyperalgesia (26). Wide electrode fields allow selective analgesia to produce effective pain paresthesia overlap and overall pain relief (27). Traditionally, four electrodes were used in SCS (26). Currently, SCS can include up to 32 individual electrodes and/or five columns of electrodes (28). The added length and number of electrodes allow multi-level spinal cord stimulation and preferential stimulation of dorsal columns over dorsal roots (1). Dorsal root ganglion (DRG) stimulation has been developed to transmit low amplitude pulses to blunt primary sensory nuclei pain transmission (29). Due to the small space near dorsal root ganglia, lead stability is enhanced, and pain response variability decreases (30). Deer et al. has shown improved response rates with DRG stimulation compared to conventional SCS therapies (30).

4. Clinical Studies

Burst SCS was first tested in a 2010 study as a novel stimulation design that could reduce neuropathic pain without paresthesia, a side effect frequently observed from spinal cord stimulation (31). Twelve patients experiencing neuropathic pain received a spinal cord electrode implant, which administered external stimulation. They obtained traditional tonic stimulation (40 or 50 Hz) and burst stimulation (40-Hz burst with five spikes at 500 Hz/burst) separately. Before and during each stimulation, pain scales were evaluated while the absence or presence of paresthesia was noted. Burst stimulation showed promising results, as the method significantly increased pain suppression, based on the VAS and McGill Short Form score, with fewer patients exhibiting paresthesia symptoms for burst (17%) vs. tonic (92%) stimulation.

A follow-up 2013 study by Ridder further evaluated the efficacy of burst stimulation by comparing testing three stimulation patterns: burst, tonic, and placebo (20). Fifteen subjects experiencing pain received a lamitrode implant and were administered each stimulation pattern for one week. After each week, primary outcomes were measured using VAS scores for low back pain (LBP), extremity pain, and overall pain. In contrast, the next outcomes were measured using VAS scores for the worst, least, and momentary pain and the pain vigilance and awareness questionnaire (PVAQ) for attention to pain and changes in pain. Pain intensity scores improved for burst SCS (back: 51%, limb: 53%, general: 55%) and tonic SCS (back: 30%, limb: 52%, general: 31%) compared to scores for placebo. Pain now, least, and worst pain improved for burst (now: 50%, least: 73%, worst: 36%) and tonic stimulation (now: 26%, least: 46%, worst: 13%). A significant improvement was observed for all measurements for burst SCS when compared

with placebo. Only burst stimulation demonstrated improved outcomes while tonic and placebo showed worse outcomes concerning attention to pain and pain changes. While there was no significant difference in back and leg pain for burst SCS and tonic stimulation, burst SCS demonstrated a significant improvement for general pain, proposing that burst SCS functions through a pathway involved with central pain processing (20).

To test the long-term safety efficacy of burst SCS, a multicenter, cross-over, randomized controlled study, the SUNBURST study, was initiated in 2013 to gain approval for use by the FDA (32, 33). One hundred participants affected by failed back surgery syndrome (FBSS) or radiculopathy were randomized to three months of tonic and then three months of burst stimulation or vice versa. Measurements were made at 1.5, 3, 4.5, and 6 months, and then study population would select their desirable treatment and be measured every six months for up to 2 years. Assessments involved using visual analogue scale for general and extremity pain, Oswestry disability index (ODI), Pain Catastrophizing Scale (PCS), Beck Depression Inventory (BPI), and checking numbness, satisfaction, and preferred treatment. The primary endpoint was measured based on the non-inferiority of burst vs. tonic, calculated by the difference in the mean general pain score at the terminal of every four months' stimulation course. The study demonstrated that burst stimulation was significant difference to tonic stimulation. Burst also showed superiority for total pain score, truncal pain scale, and extremity pain. More participants preferred burst stimulation compare to tonic stimulation. After twelve months, 68% of participants chosen burst stimulation, 24% selected tonic, and 8% of participants had no priority in stimulation.

To evaluate an energy-conserving strategy for burst SCS, a 2018 randomized controlled trial tested different microdosing stimulation techniques for burst SCS compared to a standard method used to treat chronic leg and back pain (34). 25 Subjects with previous experience using burst dorsal root (burstDR) SCS for leg and back pain were selected to receive three 2-week stimulations conducted in random order: BurstDR SCS, microdosing A (5 secs burstDR with 5 secs no stimulation), and microdosing B (5 secs burstDR alternating with 10 secs no stimulation). Primary outcomes were evaluated by a change in pain ratings on the VAS. In contrast, secondary outcomes were measured by a change in score for quality of life, satisfaction, and preference using the EQ-5D Scale. There were no significant differences in VAS and EQ-5D scores when comparing standard burst, microdosing A, and microdosing B stimulation techniques. However, microdosing A and B had slightly higher satisfaction levels and were generally preferred over the standard burst stimulation (34).

Using results from the SUNBURST trials, a 2019 study evaluated if burst stimulation was more efficacious than tonic stimulation in decreasing the reported pain (35). Based on existing data from the 100 participants enrolled, researchers determined a significant correlation between the amplitude of burst and tonic stimulation and self-reported pain scores and psychosocial factors. Self-reported pain was evaluated 6, 12, 18, and 24 weeks post-stimulation using VAS, PCS, and the SF-36v2 Health Survey (SF36v2). Data analysis of reported pain scores revealed a positive correlation for burst amplitude for "worst" and "trunk" pain on the VAS, a positive correlation for the domains of "role physical" "bodily pain", "general health" for SF36v2, and a positive correlation for scores on the PCS. The results aligned with the original hypothesis that lower burst spinal cord stimulation amplitudes could significantly increase pain suppression in subjects (35).

A second post hoc analysis conducted on the SUNBURST trial evaluated how tonic and burst stimulation affected the rate of opioid consumption for subjects (36). Out of the original 100 patients from the SUNBURST study, researchers analyzed 69 subjects who took opioid medications at baseline and evaluated opioid consumption both originally and 12 months after implantation as a primary endpoint. Analysis of opioid consumption was further specified based on CDC markers (less than 50, 50 - 90, 90 - 120, more than 120 morphine milligram equivalent (MME) per day) and preferred stimulation mode (tonic or burst). Subjects had significantly lower opioid consumption at 12 months than baseline (53.94 vs. 79.19 MME, $P = 0.008$). At 12 months, 15.9% of patients originally taking opioids discontinued consumption, while the patients ratio taking more than 120 MME per day reduced by 61.7% compared to baseline (36).

To further expand on the known efficacy of burst SCS, the TRIUMPH study was initiated in 2018 to focus on evaluating psychosocial outcomes unrelated to pain relief (37). A total of 269 patients exhibiting chronic truncal and lower extremity pain were enrolled across 22 centers to receive an implant and be evaluated at 6 and 12 months. Psychosocial and functional outcomes linked to pain relief and quality of life were assessed. One-year outcomes from burst SCS showed improvements for all psychological measures, with the most significant impact being catastrophizing and depression. Catastrophizing and depression are affective components that are associated with pain-related beliefs, contributing to poor prognoses and quality of life for subjects with chronic pain (37).

A post-hoc analysis conducted one year after the conclusion of the TRIUMPH study assessed if burst SCS efficacy varied with psychological distress in chronic pain subjects (38). Specifically, the study addressed how psycho-

logical symptoms, like catastrophizing and depression, could negatively impact outcomes from spinal intervention. Study data were identified as subgroups: those with distress, and without high distress. Psychological distress (PD) was defined as a baseline score of at least 30 on the PCS and at least ten on the Patient Health Questionnaire Depression Scale (PHQ-9). If PCS and PHQ-9 were below these scales, subjects were classified as non-distressed (ND). Twenty-four months after implant, 71% of subjects had not clinical catastrophic status, and 58% had not clinical depression. Health-related quality of life was 82% superior in the PD group after two years, similar to that of the ND group. Patient-reported pain relief was similar for each group, with 58% for the PD group vs. 61% for the ND group. The results demonstrated that burst SCS could be as effective in a chronic pain patients for those with high psychological problems versus those who did not have distress (38).

A 2020 study by Royds et al. confirmed the efficacy of burst SCS, discovering a supraspinal mechanism with altering synapse assembly and immune regulation by modulating the CSF proteome (39). Four cases with neuropathic pain were chosen for SCS with their CSF sampled before SCS implantation and two months after continuous stimulation. Samples were evaluated for T cell frequencies analyzed by flow cytometry, proteome analysis was done using mass spectrometry, and other components were measured by ELISA, including secreted cytokines, chemokines, and neurotrophins. All patients had a > 50% reduction in pain after eight weeks of burst SCS. Additionally, the four subjects had a significantly lower expression of proteins involved in synapse assembly and immune regulation. The study proposed that changes in the proteome of spinal fluid detail a physiological mechanism behind pain suppression caused by burst stimulation (39).

5. Conclusions

SCS has been FDA-approved for treatment for a initial indication of neuropathic extremity pain that is resistant to more conservative medical therapy (13). Additional benefits of SCS therapy include reduced narcotic use, improved quality of life, and more opportunity for returning to work (3). The disorders qualified for treatment include neuropathic, post-surgical, post-amputation, osteodegenerative, and pain related to vascular disease (13, 15). Some of the most frequently cited conditions for treatment of SCS include failed back surgery syndrome, CRPS Type I and Type II, and post-herpetic neuralgias.

SCS targets hyperexcitable central neural pathways and efferent sympathetic transmission related to CRPS

pain signaling (6). Despite these successes, some CRPS patients do not experience adequate relief, or pain control diminishes over time (1). Current studies also suggest that post-herpetic neuralgia can be managed through SCS therapy. Post-herpetic neuralgia produces painful paresthesia along the dermatomal pattern affected by the Herpes Simplex virus, which has shown persistent resistance to analgesic pharmacotherapy (8).

While many of these painful, difficult to treat conditions, SCS has provided adequate therapy in cases refractory to conservative management and may lead to prolonged pain relief, decreased narcotic requirement, and improved quality of life (3). Burst SCS has been shown in available studies to be non-inferior to the traditional SCS, which can cause pain paresthesia in patients who already have chronic pain. Burst SCS does not seem to cause or need the paresthesia seen in traditional SCS, making SCS not tolerable to patients. Moreover, some studies suggest that burst SCS may decrease opioid consumption in patients with chronic pain. This can make burst SCS an extremely useful tool in the battle against chronic pain and the raging opioid epidemic. As of now, more research needs to be performed to further delineate the effectiveness and long-term safety of this device.

Footnotes

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