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Protocols of spinal cord stimulation: mechanisms, clinical outcomes, and indications

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Abstract:

Several studies have shown that spinal cord stimulation (SCS) is a very effective way to treat chronic pain when other treatments, such as medications and surgery, have not been effective. This study examines the mechanics, clinical results, and particular indications of the three main SCS protocols: burst, high-frequency, and tonic stimulation. Based on the gate control principle, tonic stimulation has been applied extensively but has several drawbacks, such as decreasing effectiveness with time. A superior treatment option for back and leg pain is high-frequency stimulation, which lessens discomfort without producing paresthesia. By modifying brain activity, especially in the anterior cingulate cortex, burst stimulation targets the affective components of pain and improves patients' quality of life. Even with SCS's advances, problems like tolerance and decreased long-term efficacy still exist. Closed-loop and data-driven intelligent SCS systems are among the future directions that will usher in a new era in chronic pain management by providing real-time modifications and individualized treatment programs.

Keywords: Spinal Cord Stimulation (SCS); Tonic Stimulation; High-Frequency Stimulation; Burst Stimulation.

1. Introduction

Pain that has no biological significance and continues even after normal tissue repair is referred to as chronic pain. This pain may be constant or occur intermittently. Individuals suffering from chronic pain often face challenges in maintaining employment, a healthy diet, engaging in physical activities, or simply enjoying life. In 2021, it was estimated that in the United States, 51.6 million adults (20.9%) experienced chronic pain, while 17.1 million (6.9%) were affected by high-intensity chronic pain [1]. The likelihood of experiencing side effects from opioid use, such as nausea or constipation, is estimated to be 78%, with the risk of severe effects like immunosuppression and respiratory depression being 7.5% [2]. Additionally, chronic pain patients who use opioids often develop a tolerance over time.

In 1967, Shealy employed SCS in a clinical setting to alleviate chronic pain[3]. This method is an advancement of Wall and Melzack's 1965 gate control theory [4]. Following the trial, it is clear that the implanted electrodes eliminate neuropathic back pain by stimulating the dorsal horn and spinal cord roots [5]. Since then, new SCS devices have been released at an exponential rate, and our understanding of spinal cord physiology has changed. Since SCS has demonstrated good therapeutic outcomes when compared to pharmaceutical or surgical therapy, chronic back pain is often treated with it. Several studies and trials demonstrate that SCS efficiently lowers pain with very few adverse effects.

Previously known as spinal stimulation, spinal cord stimulation (SCS) is predicated on the “gate control hypothesis regarding pain transmission”. A hypothesis outlining how the dorsal horn serves as an entrance point for pain signals and how central brain networks control them was put forward by Melzack and Wall in 1965. According to this theory, pain occurs when noxious stimuli activate thin fibers (A-δ and C), thereby opening the door to nociception. On the other hand, when A-β somatosensory input fibres with a large size form complexes in the dorsal horn, nociceptive signals are inhibited, thereby closing the door to nociception. Spinal cord stimulation is divided into three categories based on the physical location of pain relief: (a) peripheral, located far from the dorsal root ganglia; (b) spinal, encompassing the dorsal root ganglia; and (c) supraspinal. Recent advances in SCS technology include the use of a modified Tuohy needle to percutaneously implant electrodes into the epidural space under image guidance. As shown in Figure 1, gamma-aminobutyric acid (GABA) relieves pain and increases serotonin, substance P, glycine, and adenosine levels in the dorsal horn of the spinal cord. SCS is typically performed using a paddle-shaped wire with 4–16 electrodes that is percutaneously placed into the epidural space during a laminectomy or laminatomy [6].

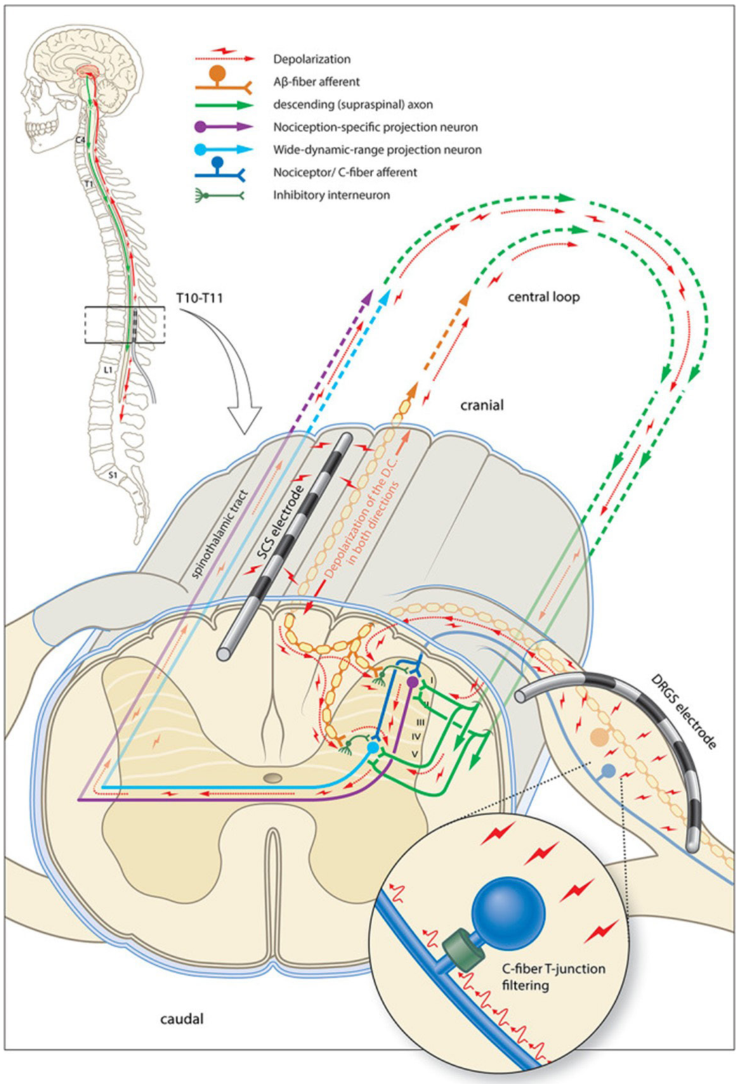

Fig. 1 The mechanisms of action of dorsal root ganglion stimulation (DRGS) and spinal cord stimulation (SCS) and the spinal nociceptive network [7]

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There are very few research examining the long-term effectiveness of SCS, despite the explosive expansion of the field. It is interesting that patients have complained about the device's declining analgesic effectiveness over time, as this is the most common reason for the device's use [8]. The development of insufficient discomfort after a positive first response and after ruling out hardware-related problems or adjustments to stimulation coverage is referred to as habituation (or tolerance) [9]. These challenges encourage people to develop new SCS waveforms, including high-frequency and burst stimulation, designed to overcome these limitations by providing pain relief without paralysis and enhancing long-term efficacy.

The aim of this article is to explore the existing scientific evidence regarding the three main types of spinal cord stimulation (SCS). The key objective is to understand the clinical outcomes, indications, and methodologies associated with each type of protocol. This paper evaluates the strengths and limitations of each approach. Additionally, the study will discuss the future advancements in SCS, including closed-loop spinal cord stimulation systems and intelligent, data-driven SCS technologies.

2. Types of spinal cord stimulation

2.1 Tonic Stimulation

Large-fiber interneurons interpret a continuous flow of pulses from tonic stimulation as paresthesia or tingling sensations. These responses effectively inhibit pain at specific levels of the spinal cord. Tonic stimulation is typically defined by low frequencies (40–100 Hz), high amplitudes that surpass the limit of sensory perception (3.6–8.5 mA), and pulse durations in the range of 300–600 μs [10]. The goal of conventional SCS (cSCS) is to get a 50% decrease in pain or more, which reaches by approximately 50% of the individuals who had the device implanted [11]. SCS electrical impulses activate Aβ fibers in the dorsal horn of the spinal cord via retrograde transmission. This triggers the spinal cord's dorsal horn's inhibitory interneurons. These interneurons, which release gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. It regulates the incoming Aδ and C fibre pain signals. As a result, the "gate" is closed, preventing pain impulses from reaching the brain, thereby reducing pain [12].

Despite its potential to reduce pain, tonic stimulation has several limitations. Firstly, only 50% or more of patients with conditions such as FBSS, CRPS, or PDPN experience significant pain relief. Secondly, the average reduction in pain is generally around 50% to 60%. Thirdly, certain areas, such as the extremities or groin, are difficult to target with tonic stimulation. Fourthly, changes in body position can alter the distance between the stimulation leads and the target area in the dorsal columns, potentially leading to discomfort due to paralysis or overstimulation. Lastly, a significant amount of electrical energy is lost to surrounding tissues [13].

2.1.1 Clinical Applications of tonic stimulation

Tonic SCS is an useful way wo cure FBSS and other neuropathic pain. This is a traditional spinal cord stimulation technique that helps patients feel less pain by covering the sensory area. According to empirical research, it has a positive effect on leg and back pain. Furthermore, even while therapy may initially significantly reduce pain, the effects of tonic SCS may eventually wear off. Long-term use of tonic SCS may lead to tolerance development. It can be essential to adjust the stimulation's parameters or move to another kind of stimulation, such as high-frequency or pulsed stimulation, if efficacy is reduced [14].

It has been demonstrated that SCS, particularly tonic stimulation, is a safe and efficient last resort for patients, particularly those with PDPN, CRPS, and FBSS, whose pain does not improve with medicine. However, there are still a lot of limitations. One of the primary drawbacks is that ankylosing SCS only provides ≥50% pain reduction, with an average drop of 50% to 60%, for 50% to 70% of patients with pain. Furthermore, both short- and long-term treatments become less effective [15].

2.2 High-Frequency Stimulation

High-frequency stimulation commonly employs frequencies ranging from 1000 Hz to as high as 10 kHz. The pulses used in this technique generally have amplitudes between 1 and 5 mA and pulse widths of approximately 30 μs [16].

Compared to tonic stimulation, high-frequency stimulation provides greater charge per second to the dorsal column by applying tonic pulses at frequencies ranging from 1 to 10 kHz. Tonic and high-frequency stimulation both produce pulses with a tonic waveform, but the two paradigms differ greatly in frequency and energy delivery, which seems to activate distinct neural pathways. The lack of paralysis might be explained by the theory that high-frequency autonomic stimulation does not activate Aβ axons in the dorsal column. Although several studies have examined the workings of it, the precise mechanism of action remains unclear [17]. Three primary working hypotheses exist at this time: (1) high-frequency autonomic stimulation causes depolarizing block, which stops action potentials from propagating; (2) high-frequency autonomic nerve stimulation induces asynchrony, causing the spinal cord "gates" to exhibit pseudo-spontaneous or random neuronal activity; and (3) High-frequency autonomic stimulation has the potential to cause temporal summation, a phenomenon in which a number of pulses that are not enough on their own to activate neurons within a certain amount of time combine to do so [18].

High-frequency SCS is better than tonic stimulation SCS in treating chronic back and leg pain. A clinical study revealed that 84.5% of patients receiving HF10 therapy experienced significant improvement in back pain, compared to only 43.8% of those treated with traditional SCS [19]. HF SCS alleviates pain without causing the uncomfortable sensory side effects, such as tingling, that some patients report with conventional SCS. This leads to greater patient comfort and satisfaction with their treatment. Additionally, the benefits of HF SCS last at least 12 months longer than those of standard SCS. Many patients using HF SCS can reduce the use of opioid, which is especially important given the risks of long-term opioid dependency.

2.2.1 Clinical Applications of high-frequency stimulation

High-frequency SCS has proven to be highly effective in managing prolonged back and leg pain, outperforming traditional low-frequency SCS in terms of pain relief. At the 12-month follow-up, 80% of patients showed a positive response compared to 50% with conventional spinal cord stimulation. HF10 SCS improves patient comfort, reduces opioid dependence, and does not induce tingling sensations. Additionally, studies have shown that patients using HF10 SCS experience higher satisfaction, a safer treatment protocol, and a lower likelihood of severe adverse effects. Overall, HF10 SCS offers a reliable and effective solution for chronic pain management.

2.3 Burst Stimulation

Compared to tonic stimulation, burst stimulation generates a larger total charge each second. Burst stimulation has a longer interval between bursts, unlike tonic and high-frequency spinal cord stimulation (SCS). It delivers many high-frequency pulse bursts to the spinal cord's dorsal column [20]. Studies have shown that the activation of pain-transmitting neurons in the dorsal horn of rats depends on the total charge within each burst.

In addition to pharmaceutical therapy, studies have shown that intrathecal infusion of GABA A and GABA B antagonists may counteract the analgesic effects of burst-type and tonic spinal cord stimulation (SCS). This suggests that GABA signaling is involved in burst-type spinal cord stimulation [21]. However, unlike tonic SCS, burst SCS exhibits a prolonged washout effect in chronic neuropathic rats. This delayed washout is attributed to the involvement and activation of supraspinal regions. In fact, burst SCS is more likely than tonic SCS to activate supraspinal areas related to emotion and motivation, according to EEG and imaging studies. Tonic SCS only engaged the lateral thalamic tracts, whereas burst SCS stimulated both the medial and lateral thalamic circuits. The former emphasizes the subjective and emotional components of pain more than the latter, which focuses more on perception and discernment [22]. Fig. 2 shows the stimulus signals of different frequencies.

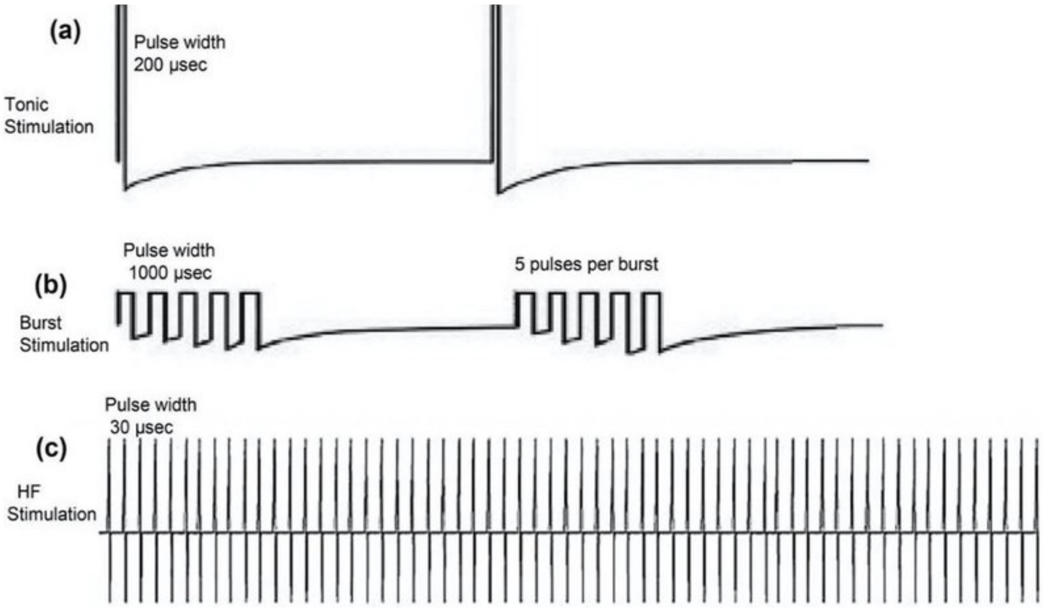

Fig. 2 Comparing high-frequency stimulation (c) and burst stimulation (a, b) with tonic stimulation (a) [23]

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2.3.1 Clinical Applications of burst stimulation

Unlike traditional low-frequency SCS, Burst SCS relieves pain mainly by modulating the brain's emotional pain processing pathways, especially neural activity in the anterior cingulate cortex. This model not only effectively relieves pain, but also improves patients' mental health, emotional functioning, and quality of life.

Studies demonstrate that Burst SCS can dramatically lower depressed symptoms and catastrophic thinking. These psychological elements frequently have a direct correlation to the persistence and exacerbation of pain. Furthermore, Burst SCS assists patients in being more active and lessening the detrimental effects of pain on day-to-day functioning. After a year, 89% of patients either reduced or maintained their opioid consumption, and 19% stopped taking them completely, according to the study. More than eighty percent of patients said they were very or very satisfied with their therapy [24].

3. Future Directions in Spinal Cord Stimulation

3.1 Closed-Loop Spinal Cord Stimulation Technology

Closed-loop spinal cord stimulation (SCS) is a new approach to treating chronic pain. Unlike traditional open-loop systems, closed-loop SCS can automatically adjust stimulation settings through continuous monitoring, allowing it to adapt to changes in patient activity or posture, which may require adjustments to stimulation dose. In order to guarantee that stimulation is both efficient and steady, the technique dynamically modifies the stimulation intensity using recorded evoked compound action potentials (ECAPs) as a feedback signal [25].

3.2 Data-Driven and Intelligent Spinal Cord Stimulation Systems

Intelligent, data-driven spinal cord stimulation (SCS) systems improve the effectiveness of neuromodulation therapies for chronic pain by utilizing machine learning algorithms, feedback loops, and real-time data analysis. These systems gather patient-specific data, such as neural activity patterns, and dynamically adjust stimulation parameters to provide personalized and adaptive pain management. By constantly tracking the patient's response to the stimulation, intelligent SCS systems enhance the precision and effectiveness of pain relief through continuous real-time adjustments [26].

4. Conclusion

In summary, spinal cord stimulation (SCS) technology shows great potential and diverse application pathways in chronic pain management. Although traditional Tonic SCS has a good effect in relieving pain, its long-term effect is limited, and some patients may gradually develop tolerance to it. By contrast, High Frequency SCS (HF SCS) and Burst SCS, with their more effective and customized pain management techniques, broaden the application domains of SCS even more. High-frequency SCS has demonstrated outstanding long-term effectiveness in treating back and leg pain, whereas burst SCS dramatically enhances patients' quality of life and mental health by modifying their emotional pain processing pathways.

With the advancement of technology, the emergence of closed-loop SCS and data-driven intelligent SCS system marks the future of pain management. Closed-loop SCS ensures the stability and continuity of stimulation through real-time monitoring and adjustment, while data-driven smart SCS uses machine learning and feedback loops to achieve more precise and adaptive pain relief. These innovative technologies provide patients experiencing chronic pain with more options and significantly improve treatment outcomes and quality of life.

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