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Spinal Cord Stimulation in Pain Management: A Review

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Spinal cord stimulation has become a widely used and efficient alternative for the management of refractory chronic pain that is unresponsive to conservative therapies. Technological improvements have been considerable and the current neuromodulation devices are both extremely sophisticated and reliable in obtaining good results for various clinical situations of chronic pain, such as failed back surgery syndrome, complex regional pain syndrome, ischemic and coronary artery disease. This technique is likely to possess a savings in costs compared with alternative therapy strategies despite its high initial cost. Spinal cord stimulation continues to be a valuable tool in the treatment of chronic disabling pain. (Korean J Pain 2012; 25: 143-150)

INTRODUCTION

Chronic pain is a leading cause for physical and emotional suffering, familial and social disruptions, disability, and work absenteeism. Neuromodulation with Spinal cord stimulation (SCS) is one of the most exciting developments in chronic pain management. It has been used for approximately four decades in treating chronic neuropathic pains that have been refractory to other conventional treatments. The technique is believed to inhibit chronic pain by stimulating the large diameter afferent nerve fibers in the spinal cord, which is based on the gate control theory of pain proposed by Melzack and Wall [1]. In 1967, Shealy [2] first inserted the dorsal column stimulator into patients suffering from cancer pain. However, it has recently been proven that applying an electrical field to the dorsal epidural space might activate a larger number of neural structures. Low-level electrical impulses, delivered directly into the spinal cord through the SCS that is inserted in the epidural space, interfere with the direct transmission of pain signals traveling along the spinal cord to the brain. Therefore, the term dorsal column stimulation was replaced with SCS. It is strategically aimed to replace the unpleasant sensory experience of pain with a more pleasing tingling sensation referred to as parasthesia [2,3]. Recently, the outcomes of SCS have improved significantly and have become a widely accepted form of therapy for chronic intractable neuropathic pain [3-6].

THE TECHNOLOGY

The SCS hardware consists of an electrode lead, an extension cable, a pulse generator, and a programmer. The electrodes that were developed initially were unipolar, and the shortcomings were apparent through its limited field of paresthesia and application. Therefore, a lead design which varied in the number of electrodes from four to eight, was subsequently developed. Currently, there are two types of electrode leads available: the Percutaneous lead and the Paddle lead. The Percutaneous electrode can be inserted via Tuohy needles and is ideal for both trial and permanent implants. The placement of the Paddle lead requires open surgery (laminotomy or partial laminectomy), but offers the advantages of greater stability and less propensity to migrate. The Paddle lead is suitable for patients with a history of lead migration or experiences where the placement of the trial lead was difficult [6].

The implanted leads are connected along extension cables that lead to the pulse generator, where the system is programmed by adjusting the amplitude, pulse width, and frequency. It has been proven that the programmable multiple-electrode arrays are superior to the single-channel devices because they allow anode −cathode guarding and polarity changes, which facilitates in optimal current steering [6]. There are two types of pulse generator systems currently available: a completely internal pulse generator (IPG) containing a battery or an IPG that is supplied by external power through a radiofrequency antenna applied to the skin. Activation and programming of the IPG occurs through an external transcutaneous telemetry device. Patients can turn the stimulator on and off, and can control the stimulation amplitude, frequency, and pulse width. The lifespan of the battery depends on the usage and the level of the utilized parameters (voltage, frequency, pulse width, etc.). With average use, fully implantable non-rechargeable pulse generators have a battery life of between 2 and 5 years. However, a new SCS system with a rechargeable power source may last up to 10−25 years. In addition, it has an advantage over the implanted system for patients requiring higher amplitudes of stimulation. As a result, the rechargeable IPG is gaining popularity due to its small size and ease of maintenance [7,8].

MECHANISM OF ACTION

The exact mechanisms of pain relief by SCS still remain unknown. The basic scientific background of the SCS trials was based initially on the Gate Control Theory of pain, described by Melzack and Wall [1]. In this theory, they proposed that the stimulation of large non-nociceptive myelinated fibers of the peripheral nerves (A−β fibers) inhibited the activity of small nociceptive projections (A−δ and C) in the dorsal horn of the spinal cord. However, it seems that other mechanisms may play a more significant role in the mechanisms of action of the SCS. In animal studies, it was demonstrated that SCS promotes the activation of gamma-amino butyric acid (GABA)−B and the adenosine A−1 receptors that lead to pain modulation [9,10]. Specifically, in neuropathic pain states, the basal levels of exciting neurotransmitters were increased partly due to a defective local GABA-ergic function. It was shown that the neurotransmitters that were known to be involved with pain modulation in the spinal cord, such as GABA, substance-P, and serotonin, were released by SCS [11,12]. In the animal pain model with sciatic nerve injury, SCS inhibited the hyperexcitability of the wide dynamic range cells in the dorsal horn [13,14]. This suggested that the predominant anti-nociceptive effects of SCS occur via A−β fibers [15,16]. SCS may also abolish peripheral ischemic pain by rebalancing the ratio of the oxygen supply and demand, thus preventing ischemia. At low levels of stimulation, SCS attenuates hyper-activity of the sympathetic nerve system as shown by anti-ischemic and anti-anginal characteristics [17]. The anti-anginal effect may also be attributed to the suppression of the central nerve system, the stabilization of the intrinsic cardiac nervous system, or the release of adenosine [17]. At increased levels of stimulation, the nitric oxide dependent release of the calcitonin gene-related peptide may play a significant role in inducing vasodilatation, leading to anti-ischemic effects [18,19].

The relative positions of the cathodes and anodes and their distances from the spinal cord were demonstrated as being the major determinants of axonal activation and paresthesia distribution. With a dual-channel pulse generator and non-simultaneous pulses, a deeper penetration of the cord without the creation of a larger electrical field is achieved [20]. Recently, the development of a transverse tripole array (+, −, +) system introduced the concept of

electrical field steering through selective recruitment of axonal nerve fiber tracts in the dorsal columns. This technique simplifies steering the paresthesia electrically through the axial back region, while minimizing the stimulation of the nerve roots [21].

INDICATIONS

SCS is particularly effective for relieving pain of the neuropathic origin. The most common indications include failed back surgery syndrome (FBSS) with radicular pain, complex regional pain syndrome (CRPS), peripheral neuropathy, phantom limb pain, angina, and ischemic limb pain [6].

Currently, the protocols for SCS implantation stipulate a pre-implantation screening trial. The percutaneous technique for electrode placement via a modified Tuohy epidural without laminectomy is less invasive. As a result, this technique easily allows for a trial simulation that assesses the suitability for a permanent implant. During the trial implantation, the patient is asked to indicate the location of the paresthesia. It is important to confirm that the resultant paresthesia overlaps with the painful area in order to achieve good analgesia. During the trial period, which can last from 3 to 15 days, the amount of pain relief is monitored with usual daily activities. The accepted benchmark for a successful trial is 50% or greater in the reduction of baseline pain. In addition, if the patient is satisfied with the results of the trial, implantation of the permanent SCS system is performed [22].

1. FBSS

FBSS is one of the most common indications for spinal cord stimulation. It is defined as a condition of persistent pain after attempted back surgery. In 2005, a systematic review of the literature cited by Taylor et al. [23] showed that SCS not only reduces pain, but it also improves the quality of life, reduces analgesic consumption with minimal significant adverse effects, and may also result in significant cost savings over time. They concluded that the level of evidence for the efficacy of SCS in chronic back and leg pain secondary to FBSS remains "moderate."

SCS and re-operation are considered treatments for FBBS. The randomized controlled trial (RCT) by North et al. [24] demonstrated that SCS is superior to re-operation for the treatment of failed back surgery syndrome. In this study, a total of 50 patients with refractory FBSS that mainly possessed radicular neuropathic pain (with or without low back pain) were randomized to either repeat back surgery or undergo SCS implantation. 45 patients (90%) were reached for a 24 month follow-up. SCS was more successful with greater than 50% pain reduction than re-operation (9 of 19 patients versus 3 of 26 patients, $P < 0.01$). Patients randomized for re-operation required an increased amount of opiate analgesics, significantly more often than those randomized for SCS ($P = 0.025$). A post 5 year term reviewing the analgesic effects of SCS on FBSS was also demonstrated by North et al. [25]. In their study, 50 patients with FBSS who averaged 3.1 operations underwent SCS implantation. At their 5 year follow-up, 47% of the patients reported a pain relief of 50% [25]. Kumar et al. [26] compared SCS with conventional medical management (CMM) in patients with FBSS, with predominant leg pain of neuropathic radicular origin. At their 24 month follow-up, 37% of the patients in the SCS group versus 2% in the CMM group achieved at least 50% in pain relief as the primary outcome ($P = 0.003$). Of the 72 patients who received SCS as their final treatment, 34 (47%) achieved the primary outcome versus 1 (7%) of the 15 patients who received CMM as their final treatment ($P = 0.02$). The 42 patients continuing with SCS (of the 52 randomized to SCS) reported significantly improved leg pain relief, health-related quality of life (HRQoL), and functional capacity [26].

2. CRPS

CRPS is a chronic pain condtion that is believed to be the result of dysfunction in the central and peripheral nervous systems. This disease is a neuropathic pain condition characterized by burning spontaneous pain, allodynia, hyperalgesia, dystrophic changes of the skin, osteoporosis, and loss of motor functions. In 2004, Kemler et al. [27] conducted an RCT to compare the effects of SCS plus physiotherapy to physiotherapy alone in patients with chronic CRPS type I. The results showed that at the two year follow-up the mean pain relief of the 24 patients with an implanted spinal cord stimulator was 3, as compared with no change among the 16 patients receiving physical therapy, which were indicated by the visual analog scale (VAS) from 0 (no pain) to 10 (the worst possible pain ($P < 0.001$). In addition, 15 of the 24 patients (63%) with SCS reported "much improvement," compared to 1 of the 16 patients (6%) receiving physical therapy ($P < 0.001$).

Although there were no clinically significant improvements in the functional status of either group, SCS resulted in significant improvements in the pain-rating index McGill Pain Questionnaire (P = 0.02) and the HRQoL for patients with an affected hand (P = 0.02) and those with an affected foot (P = 0.008) [27]. However, a 5-year follow-up analysis revealed that the pain-alleviating effects of SCS in patients with chronic CRPS-I diminished over time, and compared to the results in a control group, this effect is no longer significant after 3 years of follow-up. Nevertheless, patient satisfaction at the 5-year follow-up remains high and 95% of the patients with an implant would repeat the SCS treatment [28].

The goal of the treatment of CRPS is to restore the use of the affected limb as much as possible. Several pieces of evidence suggest that SCS should be included in the treatment algorithm for patients with CRPS [5,6]. Specifically, if patients do not respond to conventional treatments within 12 to 16 weeks, a trial of SCS should be considered [29].

3. Refractory angina pectoris

Refractory angina pectoris has been defined as severe chest pain due to coronary artery disease that is not relieved by conventional treatments, i.e., pharmacological, surgical, or both. SCS appears to be the most promising technique for patients with refractory angina. The first clinical application of SCS for intractable angina was performed by a group from Australia who reported a decrease in both angina attacks and nitrate use [30]. Recently, SCS was shown to improve the New York Heart Association functional class, reduce hospital admissions, and improve the quality of life [31,32]. These improvements appear to be persistent without causing additional risks to the patients. Mannheimer et al. [33] compared the effects of SCS and the coronary artery bypass graft (CABG) surgery in high surgical risk patients. Both treatment methods caused a significant decrease in the frequency of anginal attacks and the consumption of short-acting nitrates, whilst the CABG group had significant exercise capacity at 6 months. However, during the follow-up period, the mortality rate was 13.7% in the CABG group and 1.9% in the SCS group. This difference in mortality was significant on an intention to treat basis (P = 0.02). Therefore, SCS can be an equivalent alternative to CABG for patients with an increased risk of surgical complications [33]. In 2010, prospective multicenter studies were performed to assess the long-term effects of SCS on angina symptoms and for the quality of life in patients with refractory angina pectoris [34]. One hundred twenty one patients were implanted and were followed up for 12.1 months. The implanted patients reported fewer angina attacks, reduced short-acting nitrate consumption, and improved Canadian Cardiovascular Society class. In addition, the quality of life was significantly improved [34].

The mechanism of action for SCS to treat angina is still unclear. The increased sympathetic tone and the noradrenaline spillover into the coronary sinus that may result from myocardial ischemia and/or pain can persist for a prolonged period of time [35,36]. This may induce an increase of myocardial oxygen, which results in the production of more myocardial ischemia or infarction It was demonstrated that SCS significantly decreases both this reflex pathway and the noradrenaline spillover [37]. In addition, SCS can produce the suppression of intrinsic cardiac neurons during myocardial ischemia, reduction in pain perception, and antidromic vasodilation [18,19,38]. For angina, the tip of the electrode is generally placed at T1 or T2 to the left of the midline. This provides paresthesia in the area corresponding to the angina pain [39].

4. Peripheral ischemic limb pain

Peripheral vascular diseases can lead to critical limb ischemia. This term refers to a condition manifested by ischemic pain at rest, ulcers, or gangrene in one or both legs due to a proven arterial occlusive disease. Patients with non-reconstructible critical limb ischemia (CLI) often require amputation. In 1976, Cook [40] first inserted SCS into patients with CLI, reporting that SCS resulted in autonomic changes and warming in the extremities. SCS has shown promise in being an ideal therapy to improve outcomes including significant long term pain relief and limb salvage in many studies [41-44]. In a prospective RCT by Jivegard et al. [42], a comparison of the effectiveness of SCS versus analgesic (control) treatment in patients with CLI demonstrated that SCS provides long-term pain relief, but limb salvage at 18 months was not significantly improved by SCS. However, a subgroup analysis of patients without arterial hypertension showed a significantly lower amputation rate in the SCS versus the control group [42]. Petrakis IE and Sciacca [45] implanted SCS in 150 patients with gangrene in severe lower limb ischemia after failed

conservative or surgical treatments. After a mean follow-up of 71 months, pain relief >75% and limb salvage were achieved in 85 patients. In 28 patients, partial success was obtained with pain relief >50% and limb salvage for at least 6 months, while 37 patients received amputations. In 2005, a Cochrane review evaluating the results of six studies, including nearly 450 patients, concluded that SCS was superior to conservative treatments in improving limb salvage and clinical situations for treating patients with non-CLI [46]. Horsch and Claeys [47] assessed pain relief, limb salvage, and skin circulation in 177 patients with non-reconstructible CLI who were receiving SCS. After a three year follow-up, significant pain relief (>75%) with limb salvage was achieved in 110 patients. The cumulative limb salvage rate was 66% at 4 years after SCS. Patients without clinical improvements generally did not show a transcutaneous oxygen tension ($TcPO_2$) increase, and frequently required major amputations [47]. Pain reduction and $TcPO_2$ increases are the selection criteria generally used for the implantation of SCS [47,48]. It was suggested that patients with a pain relief of more than 50% and an increase of $TcPO_2$ of more than 15 mmHg after the trial stimulation were considered for full implantation of SCS [49].

COST EFFECTIVENESS OF SCS

Data available so far have shown that despite the initial high costs, SCS is cost-effective for the long term. Manca et al. [50] compared HRQoL and the cost implications of SCS plus CMM versus CMM alone in 100 patients with FBSS. Over the first 6 months of trial and compared to CMM alone, the HRQoL in the SCS group was markedly better, although additional healthcare costs were required. Kemler et al. [7] assessed the cost-effectiveness of the SCS plus CMM compared with CMM alone in patients with CRPS, while also inverstigating the cost-effectiveness of non-rechargeable versus rechargeable IPGs. In selected patients with CRPS, SCS was cost-effective at a willingness to pay the threshold of £30,000, while the incremental cost-effectiveness of SCS compared to CMM was £3,562 per quality-adjusted life-year. When the longevity of the IPG is 5 years or less, a rechargeable IPG is more cost-effective than a non-rechargeable IPG [7,8]. Yu et al. [51] conducted a study about the efficacy and cost benefits of SCS for refractory angina. At 18 months of ob-

servation, SCS in 24 patients with refractory angina pectoris decreased the hospitalization rates and the duration related to coronary artery disease. The total costs of the SCS procedure were recovered within 16 months after the implantation, which is less than 40% of the device's life span [51]. Klomp et al. [44] found that the total cost over two years were 28% higher in patients with CLI who received SCS than that of the conservative group. The initial costs in the SCS group were high, with all other costs evolving similarly in both treatment groups. Most of the costs were associated with staying in the hospital and rehabilitation [44].

COMPLICATIONS

The complications of SCS have been reported to be at 30% to 40%, which increases the overall costs of the procedure management and decrease the efficacy of SCS [52,53]. The recent literature review by Turner et al. [52] states the following incidences of complication: additional revision (23.1%), hardware malfunction (10.2%), infection (4.6%), biological complications other than infection or local pain (2.5%), pain at the pulse generator site (5.8%), and stimulator removal (11.0%). Mekhail et al. [53] reviewed the 707 consecutive cases of patients who received SCS therapy. Hardware-related complications were common (38%) and included lead migration (22.6%), lead connection failure (9.5%), and lead breakage (6%). Revisions or replacements were required for these cases. Biologically related complications included pain at the generator site (12%) and clinical infection (4.5%). There was one case of seroma noted without evidence of infection [53].

Complications are generally minor with proper expertise. The most common complication was found to be hardware problems which included electrode migrations. Percutaneous leads have a higher incidence of migration than that of Paddle leads. The lead migration occurs frequently within the first few days after the implantation (11-45%) [54]. The most significant complications were associated with neurological damage due to intraoperative root or spinal cord injury or infection. Epidural hematoma can also cause postoperative neurological deficits [55]. To prevent infection, a strict sterile technique, reduction in surgical time, and perioperative prophylactic antibiotic therapy should be considered during the implantation, while it is generally recommended that a single dose of an-

tibiotic be administered intravenously prior to the procedure [56,57]. Persistent pain at the implant site must be carefully differentiated from an indolent infection of the implanted equipment. The infections should be managed with antibiotics and the removal of the infected hardware [53]. Accidental punctures of the dura mater, with resultant leakage of cerebral spinal fluid (CSF), during the implantation of the SCS resulted in temporary malfunction of the SCS lead and post-dural puncture headache (PDPH) [58].

In cases of PDPH following SCS implantation, conservative management as an initial treatment strategy should be tried. However, in cases of refractory PDPH, epidural blood patches are recommended [58]. Painful stimulation, which necessitates either repositioning or removal of the electrode, has also been reported in a number of cases [54].

CONCLUSION

SCS has been established as an effective treatment in a number of painful syndromes. SCS can provide long-term pain relief with a concomitant improvement in the quality of life, daily function, and patient satisfaction, although the initial costs may be high. The key elements for the success of SCS are dependent on: understanding the mechanism of the action of SCS, mastering the surgical techniques involved in performing SCS, careful selection of patients, the improvements in matching electrode placement to sites of pain, and the advent of multipolar stimulation systems. The assessment and control of emotional and cognitive variables allows better adjustment for the patients to the SCS technique, limits the chances of the therapy being applied inappropriately, and enhances the satisfaction of the intervention in the long term.

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