Review Article

Spinal cord stimulation for patients with inoperable chronic critical leg ischemia

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BACKGROUND: Because of the prevalence of diabetes, the treatment of diabetic foot is still challenging. Even an exactly proved effective and practical method can't be listed except vascular surgery which is not a long-term way for it. Spinal cord stimulation (SCS) is a very promising option in the treatment algorithm of inoperable chronic critical leg ischemia (CLI).

DATA SOURCES: We searched Pubmed database with key words or terms such as "spinal cord stimulation", "ischemic pain" and "limb ischemia" appeared in the last five years.

RESULTS: The mechanism of SCS is unclear. Two theories have emerged to interpret the benefits of SCS. Pain relief from SCS can be confirmed by a majority of the studies, while limb salvage and other more ambitious improvements have not come to an agreement. The complications of SCS are not fatal, but most of them are lead migration, lead connection failure, and local infection.

CONCLUSIONS: SCS is a safe, promising treatment for patients with inoperable CLI. It is effective in pain reduction compared with traditional medical treatment.

KEY WORDS: Spinal cord stimulation; Critical leg ischemia; Pain reduction

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INTRODUCTION

Because of the increasing prevalence of diabetes, the treatment of diabetic foot has been a challenge.^[1-3] Except for vascular surgery, there is no effective and practical treatment for this condition. Spinal cord stimulation (SCS) is a potential option. In this article we review the studies published in the last five years, and try to find the exact effect of SCS in the treatment of peripheral ischaemic disease such as diabetic foot.

It is conservatively estimated that the global prevalence of diabetes is no less than 9.6%,^[1] and approximately 15%^[2-3] of the patients have developed diabetic foot as a result of chronic critical leg ischemia (CLI). In 2006, the total prevalence of chronic CLI in a population aged from 40 to 69 years in Norway

is 0.24%, with an increase with age.^[4] It is reported that about 10%-30% of patients with CLI would die within 6 months of its onset.^[5] Vascular surgery is the therapy of choice. Nevertheless, quite a few patients are unsuitable for operation. Despite technical progress, the treatment of patients with inoperable chronic CLI is still challenging; most of the patients have to undergo amputation:^[6-9] 33% at 6 months and 51% at 2 years.^[10] SCS has been recommended to treat ischemic pain and prevent amputation in patients with inoperable CLI. But high cost and complications of SCS should be considered for the patients. We searched in Pubmed database with key words "spinal cord stimulation", "ischemic pain" and "limb ischemia" appeared in the last five years.

History of SCS

On the World Diabetes Day 2005, the World Health Organization reported that every thirty seconds a lower limb is lost to diabetes somewhere in the world, but at least 50% of all diabetic leg amputations can be prevented. It is very important to evaluate the value of SCS in treating chronic CLI patients, for whom surgery has no realistic chance of success.

SCS was first described by Melzack and Wall^[11] in 1965 and used in spine-related disorders to relieve neurogenic pain, which is based on the gate-control theory of pain. And in 1976 Cook^[12] first reported its efficacy in control of ischemic pain associated with peripheral disease and diabetic vasculopathy. SCS aims to change perception of neuropathic and ischemic pain by stimulating the dorsal column of the spinal cord with an implanted stimulator. It is simply composed of implanted leads in the epidural space, a generator and controller implanted under the skin of the abdomen, and an extension cable that connects them.^[13] To date, SCS has been used in clinical practice for more than four decades. It has been reported that for the treatment of neuropathic conditions such as failed back surgery syndrome and complex regional pain syndrome type I, SCS is better than conventional medical treatment or reoperation in reducing pain.^[14-18] Moreover, SCS is effective in delaying refractory angina pain onset during exercise in a short-term follow-up.^[19-20] Whereas the power to detect clinically meaningful differences in ischemic pain trials is still quite inadequate.^[13, 21-25] In recent years, research into the therapeutic effect of SCS in control of ischemic pain secondary to peripheral vascular disease particularly in inoperable CLI has become a hot topic around the world. For more than ten million patients, it would be good news if the curative effect of SCS on CLI has been confirmed clinically.

Mechanism of SCS

Although the clinical benefits of SCS are clear and its success rate remains high, the mechanisms have not been completely understood. Melzack and Wall^[11] first suggested a new theory in 1965. It is called gate-control theory that SCS stimulates the afferent fibers of the dorsal column by closing the gate of pain transmission to reduce pain. But there is little evidence that SCS influences nociceptive pain; pain relief in peripheral vascular disease is presumably secondary to something else. Until now, two theories can explain the effects of SCS. One is the antidromic mechanism.

Current knowledge supports this hypothesis that, at the spinal L2-5 segments, SCS activates interneurons containing extracellular signal-regulated kinase (ERK), protein kinase B (AKT) and possibly other intracellular signaling molecules, and subsequently stimulates the spinal terminals of transient receptor potential vanilloid receptor-1 (TRPV1) containing sensory fibers. The neural information is transmitted from the site of stimulation in the spinal segments to the nerve endings in the peripheral tissues, and results in the production and release of vasodilators, including calcitonin-gene-related peptide (CGRP). CGRP, as the most powerful vasodilator, leads to SCS-induced vasodilation directly. And the subsequent release of NO may be associated with vascular smooth muscle relaxation and peripheral blood flow increase in response to SCS. Another theory is that SCS induces decreased sympathetic efferent activity, and subsequently reduces vasoconstriction and enhances blood flow in the lower limbs and feet. This is called the sympathetic mechanism. The two mechanisms are complementary, and the balance between them is affected by tonic sympathetic activity, SCS intensity, and individual patients or animal strains.^[26-31]

In general, the frequency of SCS used clinically is 50 Hz. A recent study^[32] demonstrates that compared with the normal frequency, SCS at 500 Hz significantly increases SCS-induced peripheral vasodilation without influencing motor threshold. Furthermore, effects of SCS at 500 Hz are mediated via activation of TRPV1-containing fibers and a release of CGRP.

Efficacy of SCS

Almost all of the studies show the pain relief after SCS treatment compared with best medical treatment. However, pain reduction is not the destination of this treatment. Limb salvage and other clinical improvements are more important, while until now results of SCS are not different from those of conservative treatment.

A meta-analysis of six controlled trials including 444 patients in 2006 showed a lower amputation rate of 11% after 12 months of SCS compared with optimum medical treatment. In addition, SCS patients required fewer analgesics and showed significant improvement.^[21] Gersbach et al^[33] followed 87 patients with inoperable CLI with a sitting/supine transcutaneous oxygen pressure (TcPO₂) gradient >15 mmHg for several years, and found that the effects of SCS persist beyond the first year of treatment and major amputation is infrequent after the second year. Diabetes and heart disease have a negative effect on the patients'

survival with limb salvage and amputation free.^[33] Studies on the effect of SCS for inoperable CLI caused by diabetes mellitus are performed. Four studies^[34] and a systematic review^[35] have shown promising pain-relief effect after spinal cord stimulation in patients with long-term diabetic polyneuropathy.

However, Simpson et al^[13] found that pain relief in CLI patents after SCS was not better than after other treatment. Specific selection criteria, for instance $TcpO_2$, may be developed for inoperable CLI patients. A systematic meta-analysis published in 2009 also showed insufficient evidence for higher efficacy of SCS compared with optimum medical treatment.^[22] Some prognostic factors of amputation in patients with CLI have been found, but there is no evidence for a better treatment in any group. Truin et al^[36] suggested that the success of SCS may be related to its timing in the development of chronic neuropathic pain, and their animal study confirmed the hypothesis. Early SCS 24 hours after appearance of neuropathic pain may result in an increased number of responders to SCS and an increased duration of the effect as compared to late SCS after 16 days.

Because the effect of SCS has not been confirmed, its cost-effectiveness is hard to determine. Klomp et al^[23] reported that the cost of treatment of CLI by SCS was higher than by other best treatments. Furthermore, there are no long-term effects of SCS.

Although SCS is thought to be promising in the treatment of CLI, its true effect and cost-effectiveness have not been proved. Large randomized clinical trials are needed before SCS can be integrated in the standardized treatment algorithm.

Safety of SCS

More than 14 000 SCS implantations are performed each year worldwide.^[37] In general, the most frequently encountered complications include lead migration and lead breakage, infections at implantation site, electrode connection and abdominal pocket, unwanted stimulations, hardware malfunction and allergy to metal. A retrospective review of 707 cases of spinal cord stimulation in 2010 showed that hardware-related complications (38%) included lead migration (22.6%), lead connection failure (9.5%), and lead breakage (6%). The biologically related complications included pain at the generator site (12%) and clinical infection (4.5%; 2.5% with positive culture). In this study, patients with diabetes had an infection rate of 9%, and non-diabetics had a rate of over 4%.^[38] Laguna et al^[39] reported bacterial meningitis as one of the

specific infections in 3.3% of the patients who underwent SCS lead implantation.

Moreover there are serious complications due to SCS, which may occur in sporadic cases. Atallah et al^[40] described a cutaneous neoplasm developing in the lead incision early in the postoperative period. Fortunately, there was no extension below the dermis, nor involvement in the underlying fascia. Then the neoplasm was removed completely. There was delayed spinal cord compression by scar tissue formation at the site of epidural electrodes implanted for SCS.^[41-42] This finding suggests that tolerance in the course of treatment may be a result of the development of epidural fibrosis.

To reduce the tissue injury caused by lead implantation, Tredway^[43] and Potts^[44] introduced a novel minimally invasive technique for spinal cord untethering, which is supposed to be safe and effective. This technique with a smaller incision and a shorter hospitalization could reduce soft tissue injury, postoperative pain, and blood loss. Zhu et al^[45] reported an anteroposterior fluoroscopic technique placing percutaneous cervical SCS leads. It is regarded as a safer approach to the epidural space, but its clinical effect is not clear.

To date, five cases of SCS in pregnancy have been reported. All of these cases delivered one or two healthy infants after the treatment. Another reported case had an abortion after 6 weeks.^[46] Lead breakage was found in a patient in her third vaginal birth following the initial implantation of SCS leads,^[47] which was considered to be due to increased abdominal girth. Since more cases are involved in conception and pregnancy, their safety should be considered when spinal cord stimulators are used.

Prospects of SCS

Despite the pain relief caused by SCS, there is no improvement after other treatments. Thus large studies should be focused on assessment of microcirculatory blood flow of skin, including $TcpO_2$ and video capillary results before and after SCS stimulation.

David et al^[48] suggested that the decision to implant a SCS permanently should not be dependent on only subjective measures of improvement, but on objective measures of absolute and delta values of $TcpO_2$. If there are no marked increases in $TcpO_2$, improvements after implantation of SCS leads should be questioned, especially in diabetic patients who have undergone autonomic neuropathy.^[49]

However, SCS is still considered as an option

for reducing the chance of amputation, when all conventional treatments fail to be therapeutically effective, especially in patients who suffer from pain or even could not live a normal life. The patient must know the risk of SCS, its complications and high cost.

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