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Spinal cord stimulation in chronic pain management

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The stimulation of the spinal cord is a procedure of neuromodulation. According to the definition given by the International Neuromodulation Society (www.neuromodulation.com), neuromodulation is "the therapeutic alteration of activity in the central, peripheral or autonomic nervous system, electrically or pharmacologically, by means of implanted devices."

The intriguing aspect of these procedures is that by interfering with the activity of the nervous system, we also virtually modify the functioning of other systems in the body, and this opens the possibility of using neuromodulation, particularly spinal cord stimulation (SCS), not just as a pain-modulating procedure but in fields different from pain treatment.

Since its first clinical application as a result of the effort of an American neurosurgeon [1], the procedure has been significantly improved from a technical point of view, and there is now a large variety of electrodes and devices that can be used according to the needs of the individual patient. The procedure is safe, but many adjustments of the position of the electrodes or of the stimulation parameters may be required; therefore, the patient as well as the physician who is going to apply such a procedure must be motivated and prepared for the necessity of frequent consultations.

The rationale for the use of SCS is based on the gate control theory published by Melzack and Wall [1]. According to the observation that nociceptive information traveling to the spinal cord in small-diameter unmyelinated C-fibers and in slightly myelinated A-delta fibers converge at the level of the substantia gelatinosa of the dorsal horn with nonnociceptive information, which travels in large-diameter myelinated fibers, the authors theorized that the fastest nonnociceptive information would be able to close the gate to the slowest nociceptive afferents at the level of their first synapsis in the cord. It is common experience that pain produced by beating against something hard is quickly relieved by a massage or by rubbing the injured region.

The Melzack and Wall theory has been revisited, but its core remains true; it has conditioned and stimulated the research on pain since its publication. Nociceptive afferents do not run freely to the brain but are processed during their travel, and the first step of this process occurs at the segmental level in the spinal cord, where nociceptive afferents are mainly conditioned by other nonnociceptive afferents.

We know now that other controls occur at other levels in the nervous system, and other targets have been and are under investigation to potentiate such inhibition of nociceptive information.

The electrical stimulation of the dorsal horn was conceived by Shealy [2] with the idea that stimulation of the posterior column of the cord, a concentration of large A-beta fibers, would antidromically close the gate to the nociceptive afferents at the spinal segmental level. It was soon realized that the stimulation was not as selective as it was supposed to be, and the procedure was more correctly termed *spinal cord stimulation*.

According to this idea, SCS should be useful for the treatment of nociceptive pain, but clinical experience has shown that this is not so. Furthermore, experimental observations on its mechanisms of action have focused attention on analgesic mechanisms different from the activation of the gate.

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In this article, the results of SCS in the most common clinical applications are summarized and speculations are made on the mechanisms based on clinical and experimental data.

Technique

Electrical stimulation of the spinal cord is obtained via electrodes positioned over the dorsal aspect of the spinal cord and connected to a pulse generator. Since its origin, the technique has been continuously improved. Shealy [2] started SCS using plate electrodes placed intradurally directly on the cord. The procedure required an open approach for a laminectomy and opening the dura. The epidural positioning of the electrode facilitated the diffusion of this therapy and increased the number of clinical observations [3,4].

As a general rule, when applied for pain control, SCS should be performed with electrodes placed in a position where electrical stimulation induces comfortable paresthesias overlapping the painful area.

Nowadays, there are different types of electrode on the market among which one can choose according to the particular clinical situation on a patient-by-patient basis. The ideal characteristics of an electrode should be low impedance, which results in a longer battery life; a shape that allows easy, quick, and safe positioning and overall stability into the epidural space once the right position has been obtained; flexibility; and resistance.

Wire electrodes can be percutaneously implanted using a Tuohy epidural needle under fluoroscopic control and local anesthesia. The percutaneous procedure allows one to test the best distribution of paresthesias during implantation in the operating room. Furthermore, the percutaneous technique makes it easy to implant more than one electrode during the same procedure, enhancing the chance of stimulating the correct target in the spinal cord [5,6].

Plate electrodes need a mini-invasive open procedure requiring general anesthesia or heavy sedation. The operating microscope is useful in positioning plate electrodes because it allows one to remove only a minimal part of the laminar bone and to open the ligamentum flavum under magnification to verify that the introduction of the plate does not cause any dural compression. Plate electrodes are supposed to be more stable in the epidural space.

Wire and plate electrodes can be uni- or multipolar, but there is a general tendency to abandon unipolar electrodes for SCS. A multicontact system provides more flexibility; increases the chances of obtaining comfortable paresthesias; and allows one to change the active contacts in case of variations of paresthesias because of electrode movements, thus reducing the need for repositioning of the electrode.

The theoretic background for improving electrode design came from the work of Holsheimer and Struijk [7], who developed a computer model of SCS. This and further studies considering many important variables, such as the distance between the electrode and the cord, position of the electrode, and anode-cathode configuration of the electrode, have led to predictions on the electrode configuration for correct paresthesias, which have been confirmed by clinical results [8,9].

Once the electrode has been put in place, a percutaneous test trial is generally performed to verify the efficacy of the stimulation. The easiest way to connect the epidural electrode to an external generator is to use a percutaneous extension that can be removed at the end of the test trial without removing the percutaneous electrode. The length of the test trial varies according to the etiology of the pain and is discussed elsewhere in this article; however, in most cases, the test trial is performed at the patient's home. At the end of the test, the electrode can be connected to a radiofrequency receiver that is placed under the skin, allowing activation of the electrode from an external pulse generator, or to a totally implantable generator that can be programmed from outside the body. If the percutaneous test trial is not successful, the epidural electrode is simply removed together with its percutaneous extension.

Implantable pulse generators need to be replaced when their battery is depleted. The duration of the battery varies according to the amount of current delivered and impedance of the system and according to the type of generator used, but its duration is usually measured in years.

There are three manufacturers actually competing in this area of technology, and new solutions and improvements are continuously being developed. An important feature is the recently developed advanced neuromodulation system (ANS) in the Genesis System. These stimulators deliver constant current stimulation, allowing more stable, comfortable, and effective paresthesias to the patient.

The goal of the procedure is to place the electrodes where the stimulation produces comfortable

paresthesias overlapping the painful area. Multiple electrode arrays with multiple contacts allow one to reach this goal more easily; because they can be reprogrammed from outside the body, it is also possible to overcome the problem of slight changes of paresthesias, reducing the need for further surgery. Conversely, by increasing the complexity of the stimulation devices, particularly the number of electrodes and contacts, the number of possible combinations (and, consequentially, the need for computer programming and dedicated professionals) is increased exponentially [10–13].

A review of the problems related to paresthesia control, technologic innovations and advances in programmability, and patient control of SCS has been published by Alò and Holsheimer [14]. For technical details of the systems available on the market, the reader can visit the web sites of the manufacturers as follows:

ANS: www.ans-medical.com
MEDTRONIC: www.medtronic.com
NEUROCOR: www.neurocor.com

Clinical applications

Spinal cord stimulation in peripheral vasculopathies

Pain affecting patients with peripheral vasculopathies is responsive to SCS. In a review of our experience dating from 1981, it was already clear that vasculopathic pain was not only alleviated but completely relieved by SCS in some cases [15].

In 1976, Cook et al [16] had already reported improvement in skin temperature, increase of plethysmographic wave amplitude, and healing of cutaneous ulcers in vasculopathic patients after SCS, and in the same year, Dooley and Kasprak [17] published an article on "Modification of Blood Flow to the Extremities by Electrical Stimulation of the Nervous System." These observations received little attention until our report in 1981 [18], in which we described the case of a patient with arteriosclerotic peripheral vascular insufficiency whose persistent and otherwise intractable pain was completely relieved by SCS. Healing of trophic ulcers, improvement of plethysmographic and rheographic indexes, and increase in skin temperature were documented in that patient, and, above all, temporary interruption of SCS as the result of a car accident was followed by the recurrence of pain and ulcers with reduction of blood flow indexes. Pain disappeared, and the ulcers were cured again after restoring SCS.

Our observations on the efficacy of SCS in patients with vasculopathic pain and its effect on peripheral blood flow were confirmed in our subsequent studies as well as in those of others, substantiating the suggestion that SCS was inducing an increase in peripheral blood flow [19–27].

The difficulty in measuring blood flow, especially in pathologic conditions, and the unfeasibility of sham studies, together with the natural evolution and progression of peripheral vasculopathies, made it difficult to convince skeptical vascular specialists. It took time to perform multicenter studies and to collect convincing data on the effect of SCS in pain caused by peripheral vasculopathies.

Remarkable work has been done by Sciacca [28], an Italian vascular surgeon. He made a retrospective analysis of 150 patients treated with SCS for nonreconstructible peripheral arterial occlusive disease and analyzed clinical and laboratory parameters useful in predicting the outcome of SCS. The value of the trascutaneus Po_2 study in predicting the results of SCS is stressed by this author; in fact, although all the patients who received a permanent device had reported pain relief during the test trial, good long-term results and limb salvage were achieved only in those who showed more than a 50% increase in Tc Po_2. Tc Po_2 change is considered a predictive factor more important than the stage of the disease and is thus recommended as a screening method during the test trial.

There are now several vascular centers in Europe using this procedure, and the efficacy on ischemic pain is reported to range from 70% to 90% in the long run [29].

Considering the high success rate, the percutaneous test trial is not performed in some institutions, and the patient is scheduled directly for a permanent implant. There is no question that SCS relieves ischemic pain and, consequently, can improve the quality of life dramatically in these patients. The course of the disease is not affected, or at least with the data available in the literature, there is no convincing evidence that it is [30]. Even though the best results are obtained in patients with rest pain and trophic lesions not exceeding 3 cm, my indication for SCS in this clinical situation is otherwise intractable rest pain (condition occurring in Fontaine stages III and IV of the disease). When extensive gangrene is present, our experience has been disappointing. My protocol includes a few days of a percutaneous test trial in all cases.

Extensive experimental work has been done by a Swedish group [31,32] to understand the basic mechanisms put in play by SCS. In rats, they showed depression of sympathetic activity in the paravertebral chain close to the stellate ganglion as a result of SCS at the level of T2.

In nonvasculopathic patients undergoing SCS for different pain conditions, Meglio et al [33] studied the interference of SCS with the central mechanisms of regulation of heart rate, demonstrating that SCS produces a reversible reduction of the sympathetic output (which was named "functional sympathectomy"). The interaction between SCS and heart rate was studied at rest; during physiologic (standing maneuver, rapid open hyperventilation, and Valsalva maneuver phase 3) and pharmacologic (isoproterenol) activation of the sympathetic nervous system; during parasympathetic activation produced by eyeball pressure, carotid sinus pressure, Valsalva maneuver phase 4, and somatostatin administration; and, finally, during parasympathetic block with atropin.

The observations clearly demonstrated that SCS affects the mechanisms of regulation of heart rate in human beings. The effects produced by physiologic activation of the sympathetic nervous system were reduced by SCS, whereas the pharmacologic activation obtained with isoproterenol was not affected because of its peripheral activity. Physiologic and pharmacologic activation of the parasympathetic system was enhanced, and its blockade was counteracted by SCS.

It was still unclear if the effects of SCS were the result of sympathetic inhibition or parasympathetic excitation, but the results of the test with isoproterenol suggested that a reduction of the sympathetic function is more prominent than an increase in parasympathetic activity. In fact, the drug acts on the peripheral β-1 receptors, inducing a marked increase in heart rate; if SCS were enhancing the parasympathetic tone, it should be able to neutralize or at least to reduce such an effect. In none of the patients who received isoproterenol before and during SCS was any counteraction apparent.

We also argued that such a functional sympathectomy occurring independently from the rostrocaudal level of the stimulating electrodes was probably the result of interaction on fibers ascending along the spinal cord rather than on descending fibers or on the thoracic sympathetic system itself, suggesting the involvement of supraspinal mechanisms. The duration of the effect and its prompt disappearance at the end of SCS were in favor a neurogenic rather than humoral mechanism.

Other important information on the interference of SCS with the autonomic nervous system and particularly with the mechanisms of regulation of blood flow came from studies on cerebral blood flow (CBF). The first observations in human beings in this field were made by Hosobuchi [34], who studied 10 patients treated with SCS for chronic intractable pain: 5 had an electrode at the C3 to C4 level, and the remaining 5 had a T8 to T9 electrode. He found the cervical stimulation was producing a significant rise in hemispheric CBF. Because such an effect of SCS was ipsilateral to the induced paresthesias, Hosobuchi argued that change in CBF was not related to an increased cerebral metabolic rate resulting from the afferent volley produced by the artificial stimulation of the spinal cord. Hosobuchi's observation was confirmed in animals by Garcia-March et al [35] and in human beings by our group [36–38]. We also studied the effects of SCS on carbon dioxide–induced CBF variations. By using increasing concentrations of carbon dioxide, we could study the interaction of SCS with the central mechanisms of regulation of CBF, and a reduction of the sympathetic outflow was again found to be at least one of the mechanisms put in play by SCS [39].

Animal studies allowed a more aggressive manipulation of the autonomic nervous system and provided further evidence of the sympathicolytic action of SCS [40]. Cervical SCS was performed in rabbits, and CBF was measured from the internal carotid artery after closure of both external carotid arteries by means of a CW Doppler and electromagnetic flowmeter at rest and during cervical sympathetic trunk stimulation (CSTS). During SCS, an increase in CBF was found in 52.4% of the animals, a decrease was found in 9.5%, and no change was found in 38%. During CSTS, a decrease in CBF was found in all the animals. The effect of CSTS was markedly counteracted by SCS in the rabbits showing increased CBF during SCS alone.

The sympathicolytic effect of the stimulation can play a role in many clinical applications, particularly in sympathetically maintained pain, peripheral vasculopathies, and angina.

Spinal cord stimulation in angina pectoris

The first observations on the effect of SCS on angina were made in patients undergoing SCS for different reasons. In 1980, Illis et al [41], reporting

the effects of SCS in patients with multiple sclerosis, noticed that pain was relieved by SCS in one of their patients who also had angina.

In 1984, we [42] observed clinical and electrocardiographic (ECG) improvement of ischemic heart disease after SCS. An ECG follow-up study was performed before and after SCS in 16 patients treated for different chronic neurologic disturbances.

Four patients had signs of ischemic heart disease on ECG, and two of them had a history of myocardial infarction with residual chest pain on exercise in spite of adequate medical treatment. All patients with ECG signs of myocardial ischemia showed a remarkable improvement with SCS. In one of them, the effect became evident during the first stimulation, and in all cases, it was progressive with time. No evidence of ECG changes during the period of SCS was observed in patients with normal ECG readings.

Interestingly, in those patients, the electrodes had been placed in the lower thoracic level to achieve paresthesias in the legs and not as we do now for treating angina in the cervicothoracic region to produce paresthesias in the chest and left arm.

This observation suggested that the effect of SCS was not merely a result of pain control at the spinal level but that an increase or redistribution of blood in the coronary bed could be argued and that the mechanism put into play was probably related to the activation of ascending fibers impinging on the central mechanisms of regulation of blood flow [33].

In 1987, Murphy and Giles [43] published the first report on the management of chronic angina pectoris not responding to other conventional therapies with SCS. In 1988, Mannheimer et al [44] reported on 10 patients with angina functional class III to IV New York Heart Association under optimal pharmacologic treatment submitted to SCS. They reported increased working capacity, decreased ST segment depression, increased time to angina, and reduced recovery time. In 1990, in his editorial in the *British Heart Journal*, Sanderson [45] stated that "the effect of neurostimulation is sometimes so considerable that factors other than mere pain relief must be involved, such as redistribution of local blood flow to ischemic areas as occurs in patients with peripheral vascular disease."

In 2003, the *American Journal of Cardiology* published [46] the results of a prospective Italian registry of SCS created to evaluate the clinical outcome of patients with severe angina refractory to medical treatment and unsuitable for revascularization procedures undergoing SCS. Of the 104 patients enrolled in the study, 83% had severe coronary artery disease. A reduction of at least 50% of anginal symptoms occurred in 73% of the patients. The Canadian Cardiovascular Society angina class improved by one or more class in 80% of the patients and by two or more classes in 42% of the patients, with a significant reduction in the rate of hospital admission and days spent in the hospital because of angina. From this study, the safety of the procedure has been shown, and it was found that there was no evidence of increased mortality in the group of patients with significant suppression of anginal episodes, confirming previous evidence that SCS does not increase the risk of cardiac death because of inhibition of angina as warning signal of ischemia.

The efficacy of the procedure was also demonstrated in patients with intractable angina pectoris and normal coronary angiography (so-called "X syndrome") [47]. Despite a good prognosis, these patients have a bad quality of life. A rigorously selected population of seven patients showed a significant reduction in the number of anginal episodes and in nitrate consumption. Time to 1-mm ST segment depression, time to angina, and exercise duration were all prolonged by SCS. Conversely, we found no change in the rate-pressure product, an established measure of myocardial oxygen consumption. We argue that the effect of SCS can be related to a redistribution of coronary blood flow rather than to a net increase in coronary perfusion.

Although the pathophysiology of X syndrome is still unclear, alterations of cardiac adrenergic function have been shown in most of these patients [48,49].

The sympathicolytic effect of SCS resulting from the interference with the autonomic regulation at a suprasegmental level can play a role, together with direct inhibition of pain transmission at the level of the dorsal horn, on its antianginal effect.

Spinal cord stimulation in neuropathic pain conditions

In contrast to nociceptive pain, neuropathic pain is defined as "the state of chronic suffering that is shown by predisposed patients after a lesion of the somatosensory system, usually, but not necessarily clinically evident" [50]. According to the location of the lesion, we can identify neuropathic pain caused by peripheral or central deafferentation. These conceptual separations

(schematizations) are useful for developing a rationale for therapeutic purposes, but clinical situations usually demonstrate a mixture of nociception and deafferentation.

Examples of the application of SCS are referred to three clinical settings of neuropathic (or mainly neuropathic) pain. Reflex sympathetic dystrophy (RSD), complex regional pain syndrome (CRPS), or neuropathic pain with autonomic disorders is an important indication for SCS.

The efficacy of SCS in CRPS types I and II has been reported by several authors. Barolat et al [51] report a success rate of 62% in their RSD patients at an average follow-up of 3.8 years.

A study by Kemler et al [52] was published in 2000. They randomized two groups of patients, one treated with physical therapy alone and the other with physical therapy plus SCS. In an intention-to-treat analysis, the patients with SCS reported a mean reduction of 2.4 cm in the intensity of pain 6 months of follow-up, whereas the patients treated with physical therapy alone reported an increase of 0.2 cm. Furthermore, the SCS group had a much higher global satisfaction scale score.

The role of a sympatholytic effect in mediating the analgesic activity of SCS is widely accepted. In a recent paper, Hord et al [53] studied the possible predictive value of sympathetic block (SB) in CRPS patients undergoing SCS.

They found that patients with a positive response to SB were significantly more responsive at the end of the SCS test trial compared with the patients who did not benefit from SB. Among the patients who underwent permanent implantation, at the 1- and 9-month follow-ups, SCS was more effective in those who had responded well to SB.

Spinal cord stimulation in low back and leg pain

Low back pain with or without leg pain is an extremely common clinical situation. Often, it occurs as a consequence of disk or facet degeneration, and it is frequently observed in patients with previous back surgery.

This pain condition is by far the most common clinical application of SCS, at least in the United States.

Neurogenic mechanisms are mainly involved in this pain condition, but nociception plays a role in some of these patients, especially when part of the pain is increased or provoked by loading.

One of the main problems of this application has been the possibility of achieving correct paresthesias not only in the legs but in the back. Holsheimer and Strujik [7] have theorized the diffusion of current from the epidural electrodes to the cord. Law [54,55], North et al [56], and Barolat et al [57] have realized and applied dual-electrode systems of stimulation to be able to produce paresthesias in the back. Apart from the system used and the electrode's configuration, there is general agreement that SCS can be useful for 50% to 70% of low back and leg pain patients. In a personal series [58] of 115 patients followed for a mean follow-up of 5 years, we found 70% of responders at hospital discharge and 51% at long-term follow-up. Furthermore, we tried to find prognostic factors useful for patient selection. No differences were found in our patient population between subjects with a history of previous back surgery and those with no previous surgery. Pain duration (more or less than 36 months) did not significantly affect our results. Pain distribution (with or without back pain) was also ineffective with regard to the outcome, but overlapping of paresthesias with pain distribution did significantly affect the results. Another important positive correlation was found in our series with the percutaneous test trial and its length. Patients who underwent a test trial that lasted more than 10 days had a better outcome compared with patients with a shorter trial period. Patients with totally implantable systems did much better compared with patients wearing a radiofrequency system.

An important work to be mentioned on this subject is the one published by North et al [59], who performed a prospective randomized study comparing SCS with reoperation in patients with so-called "failed back surgery syndrome." After 6 months, patients were allowed to cross from one group to the other. It came out that 67% of the reoperated patients required crossover to the SCS group, whereas only 17% of the SCS group required a new operation. The difference was statistically significant.

Comparing the results obtained in their patient population during the last decade with their previous 20 years of experience, Lazorthes et al [60] found that the results of the test trial had definitely improved from 47% to 60%. Their main indication was chronic lumbosacral radiculitis after back operation, and the success rate was stable at 74%. They stress the importance of patient selection.

In 354 patients with neuropathic sciatalgia at long-term follow-up (mean of 112 months), Blond et al [61] report 78% with excellent (49%) and good (29%) results. A global approach with

a multidisciplinary team, accuracy in electrode positioning, and continuous clinical and technical surveillance is suggested to achieve good results.

Spinal cord stimulation in spinal cord injury pain patients

Pain in spinal cord injury (SCI) patients is a difficult condition to treat, and SCS seems to be of little use in paraplegic pain [62]. SCI patients usually report various patterns of pain, which are affected in different ways by SCS. In 1995, we published [63] the results of our experience with SCS in paraplegic pain patients: 75% analgesia was reported at the end of test trial by 40.1% of our patients, but at 3 years of follow-up, the success rate was only 18.2%. In our experience, painful spasms and constrictive pain in the transitional zone were relieved in 38% and 50% of patients, respectively, whereas allodynia and burning pain were much less responsive.

Looking at the relation between the effect of SCS and the quality of pain, neurologic status, type of lesion, and electrode level above or below the lesion, we found that an important condition required for success was the relative integrity of the dorsal column. Partial preservation of the spinothalamic tract is also important; in fact, Beric [64] found worsening of pain with SCS in SCI patients with a good dorsal column and absent spinothalamic tract.

A relevant paper aimed at improving patient selection in neuropathic pain conditions has been published recently by Sindou et al [65]. The rationale of this work is that the prerequisite for SCS to be effective is the availability of a significant amount of dorsal column fibers to stimulate. Based on the common experience in clinical practice that SCS cannot exert its inhibitory effect on pain if there is a large disruption of the dorsal columns, Sindou and his group propose to use somatosensory evoked potentials (SSEPs) and, more specifically, central conduction time (CCT) to evaluate the functional integrity of dorsal column accurately and noninvasively. At the end of their study, they conclude that in patients complaining of pain because of a lesion located central to the dorsal root ganglion, it is essential to investigate the integrity of the dorsal column with SSEPs. If CCT is abolished or markedly reduced, the patient should not undergo SCS. If CCT is normal, the patient can be selected for SCS without the need for a percutaneous test trial.

When the lesion causing pain is located distal to the dorsal root ganglion, the patient can be a candidate for SCS, and a preliminary test trial is suggested only if there is an allodynic (or hyperpathic) component of continuous pain.

The results obtained by Sindou et al [65] must be taken into consideration by everyone involved in SCS; they stress the role of clinical neurophysiology in neuromodulation as well as in neuroablative procedures.

Another interesting perspective in SCS is the search for drugs able to increase the efficacy of the stimulation. The Karolinska University group has been involved for many years in experimental studies on the pathophysiology of neuropathic pain and on the neurochemical mechanisms underlying the analgesic effect of SCS [66]. They have demonstrated that at least part of the analgesic effect of SCS is a result of antidromic activation of low-threshold fibers in the dorsal column, which, by affecting neurotransmitter release, reduces the hyperexcitability of the deafferentated wide dynamic range neurons [67,68].

Microdialysis studies [69] have shown that SCS produces an increase of gamma-aminobutyric acid (GABA) and a reduction of excitatory amino acids in the dorsal horn of allodynic rats. Wallin et al [70] have shown that gabapentin, a drug whose efficacy in neuropathic pain has been related to an increase of GABA synthesis (thanks to the activation of the enzyme catalyzing the conversion of glutamate into GABA), potentiates the effects of SCS in rats with tactile allodynia when administered at a low subeffective dose. They conclude that "the combination of neurostimulation and low doses of pharmacological agent, such as gabapentin or its precursor pregabalin, may provide a useful strategy for the treatment of neuropathic pain."

The GABA(B) receptor agonist baclofen has shown synergistic activity with SCS in animal studies [71,72] and in clinical trials [73].

GABAergic and adenosine-related mechanisms conceivably represent only a fraction of a multitude of those available for possible modulation by receptor activation involved in SCS. A further exploration of the SCS mode of action and the pathophysiology of neuropathic pain is a prerequisite for developing new means of improving the therapeutic efficacy of SCS and for identifying patients most likely to respond to such treatment.

Complications

SCS is nondestructive, but it is invasive and requires a minor surgical procedure. Neurologic damage can potentially occur, but the main

complications described in the literature are related to electrode dislodgement, fractures, malfunctioning of the system, and infections. All these are minor complications and sometimes can be overcome without the need for further surgery. Nevertheless, the frequency rate of complications can be more than 20%, and the patients, particularly pain patients suffering for years, can be extremely reactive to problems related to the neuroprosthesis and can decide to abandon this form of therapy at the first difficulty. This should be taken into consideration when selecting patients for SCS. Their active cooperation and the support of their families must be acquired.

Summary

As a general rule, even though it is always difficult to predict the efficacy of a method in a single patient, we consider SCS in every nonmalignant chronic pain patient when other conservative treatments have failed.

After three decades of clinical experience with SCS, we have learned a lot about its efficacy in different pain conditions and have made great technical progress with the materials and surgical procedures.

Acceptance of the technique was slow at the beginning; however, we must be aware of the problems related to the application of a therapy that cannot be shamed, and thus the necessity of performing studies that include large numbers of patients. This is even more complicated when dealing with pain patients because of the well-known multifactoriality of pain. Nowadays, every algorithm for the treatment of different pain conditions includes SCS; consequently, every pain center should be able to offer this therapy in its treatment program.

This article discusses what has been learned so far with regard to SCS, but there is a lot more to learn about this technique as well as about other types of neuromodulation procedures.

As mentioned in the introduction of this article and discussed in the section on the effects of SCS, particularly in clinical applications like peripheral vascular disease and angina, the results of the interaction with the function of the nervous system can be observed in other systems in the body affecting pathologic conditions that are of interest to different specialists. Only the strict cooperation of different medical disciplines can provide substantial help in acquiring knowledge about the mechanisms put into play by SCS and the possible extension of its clinical applications. The complexity of the procedures of neuromodulation and the theoretic background needed for safe and proficient clinical use and for progress raise the issue for medical schools of offering courses in this new discipline.

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