

Electrical Neuromodulation in Chronic, Intractable Pain

1. Introduction

Many people suffer from chronic pain, which is defined as pain that persists continuously for at least two weeks. Chronic pain may have different origins, and is accordingly named neuropathic pain (due to peripheral nerve injury), noxious pain, inflammatory pain and sympathetic pain. Combinations may be present as well. Many treatment modalities have been developed over the years, such as pharmacological, physical, psychological, cognitive and surgical (ablation, decompression) approaches to pain management.

Despite all treatment modalities available, a significant group of patients does not respond to any of these methods. If these patients have chronic, intractable pain of primarily neuropathic origin there are still alternative methods, by which electrical stimulation is applied to the nervous system. These neuropathic pain syndromes include peripheral nerve injury and deafferentation, dorsal spinal root, ganglion and plexus lesions, postamputation pain (phantom pain), reflex sympathetic dystrophy (RSD), causalgia, spinal cord injury and failed back surgery syndrome (FBSS, low-back and sciatic pain). Stimulation methods used for the treatment of neuropathic pain of peripheral origin are: *spinal cord stimulation* (SCS) with implanted devices, *peripheral nerve stimulation* (PNS) with implanted devices and *transcutaneous electrical nerve stimulation* (TENS) with cutaneous, or skin electrodes. SCS is applied to the dorsal columns of the spinal cord, which include cutaneous nerve fibers originating from all segments up to the stimulation level and is thus appropriate for both segmental and complex pain syndromes such as FBSS, RSD and other chronic *complex regional pain syndromes* (CRPS). PNS is applied directly to a nerve in an upper or lower limb at a position proximal to the pain region and is only appropriate when this region is limited to part of the limb. The same is true for TENS, which is applied by an electrode on the skin over the peripheral nerve corresponding to the pain.

SCS, PNS and TENS are clinical methods based on neurophysiological evidence referred to as the “gate-control” theory of Melzack and Wall, which was first published in 1965. This theory postulates that the activity (spike rate) in large, primary somatosensory nerve fibers ($A\beta$ -fibers) modulates the activity of neurons in the dorsal horns which transmit noxious information to the brain. When the spike rate of $A\beta$ -fibers is increased either physiologically (by increased sensory input) or artificially (by electrical stimulation) the activity in noxious pathways is reduced, resulting in a diminished or even abolished pain perception. Due to the inverse relation between threshold stimulus and nerve fiber diameter only large ($A\beta$) fibers are activated, so that the level of analgesia can basically be modulated by the rate of the electrical pulses applied. In the 1970's, it was demonstrated that electrical stimulation results in the release of pain modulating molecules from the pituitary gland. Known as endorphins, these molecules interact with cells in the brain to cause pain suppression. So, the application of electrical stimulation can simulate the body's endogenous pain suppression mechanisms.

SCS, PNS and TENS are accompanied by a tingling sensation (*paresthesia*) in the body area(s) corresponding to the stimulated nerve fibers. An important condition for complete analgesia is that the stimulation induced paresthesia covers the pain area completely. Analgesia follows immediately when appropriate stimulation is given.

The use of electrical stimulation to suppress pain requires the patient's access to the stimulation, as needed, on a 24 hour/day basis. TENS applications provided only during clinical visits [i.e. 3 times per week for 20 minutes on each clinical visit] cannot be expected to provide significant pain relief.

2. Spinal Cord Stimulation

2.1. Hardware

About 14,000 SCS implantations each year are presently performed worldwide on chronic pain patients, of which a vast majority is in North America, the European Union and Australia. Almost all SCS systems are produced by two US companies: Medtronic, Inc. (Minneapolis, MN) and Advanced Neuromodulation Systems, Inc. (Allen, TX).

Two different types of SCS systems are commercially available: transcutaneous and fully implantable systems. Transcutaneous, or radiofrequency (RF) systems consist of a receiver implanted subcutaneously and connected to the spinal electrode(s) by a cable. Both electrical power and pulse data are transferred through the skin by an RF transmitter coil overlying the receiver. RF systems were the first ones on the market and they are still in use, particularly when rather high stimulation currents are required. Fully implantable pulse generators (IPGs) are battery powered and programmable by an external device. The IPG is connected to the spinal electrode(s) by a cable. Most patients prefer an IPG instead of an RF system, because with the latter they are always reminded of the external coil, receiver and batteries. In addition, it may be difficult for a patient to position the transmitter coil correctly over the receiver. Due to the limited battery life an IPG has to be replaced every 2-5 years, depending on the amplitude and rate of the pulses applied.

All pulse generators are voltage controlled and provide rectangular, biphasic, charge-balanced pulses of adjustable rate and duration. Most systems have one channel, which means that all metal contacts on the electrode(s) connected as anodes are at the same voltage, as well as all contacts used as cathodes. When e.g. three contacts are used as anodes, all provide simultaneous pulses of the same voltage. Unipolar stimulation can only be applied with an IPG, where its metal case can be used as a distant anode. Some recent pulse generators have two channels providing alternating pulses to different, or partly overlapping sets of electrode contacts. In this way complementary pain areas can be covered with paresthesia.

Basically two types of electrodes are commercially available: *percutaneous electrodes* and *plate (surgical) electrodes*. A percutaneous electrode consists of a cylindrical, flexible polymer tube with an outer diameter of approximately 1.3 mm, with four or eight thin platinum rings mounted near the tip. These thin platinum contacts are generally 3 mm long and are separated by 4 or 6 mm (edge-to-edge). Each contact is connected to a flexible, insulated metal wire inside the polymer tube. A plate electrode consists of a flat polymer strip with four or eight platinum contacts mounted on one side. For a long time these plate electrodes included an array of four round contacts of 4 mm diameter, separated by 6 mm. Recently plate electrodes with smaller, rectangular contacts in one or two arrays of four or eight contacts have been introduced. When the electrode has two arrays, these are placed either in parallel or offset. The flat plate electrodes have a width of about 8 mm and a length of about 40 mm.

2.2. Surgical and test procedures

It is common practise to perform a trial stimulation with a disposable percutaneous electrode. During a period of 1-2 weeks this electrode is connected percutaneously to an external, programmable pulse generator to test whether the patient perceives paresthesia in the pain area and significant analgesia. If so, a permanent percutaneous or plate electrode is implanted and connected to a subcutaneous IPG or RF receiver. An alternative trial method is to connect an electrode designed for permanent implantation by a temporary percutaneous cable to an external pulse generator.

Percutaneous electrodes are inserted medially into the dorsal epidural space under local anesthesia and fluoroscopic control via a canula between two spinous processes. The electrode is generally pushed rostrally up to a vertebral level slightly above the expected optimal position and is then pulled back smoothly during perioperative test stimulation until the patient perceives an adequate distribution of paresthesia. Implantation of the IPG or RF receiver in the abdominal wall and tunneling of a connecting cable to the electrode are performed under short-lasting general anesthesia or sedation. Implantation of a plate electrode is usually performed under

general anesthesia. A plate electrode is inserted into the dorsal epidural space via a small laminotomy and often under fluoroscopic control. When the electrode is placed the patient can be awakened (under local anesthesia of the wound area) to optimize the electrode position by trial stimulation. When correctly in place the plate electrode is sutured to the dura or a ligament.

Positioning an epidural electrode at the radiological midline under fluoroscopic control is generally an inappropriate method, because the vertebral midline and the spinal cord midline may differ up to 2 mm. Whereas an electrode position at the spinal cord (“physiological”) midline corresponds to bilateral, symmetrical paresthesia, a position just 1-2 mm aside results in asymmetrical or even unilateral paresthesia. Therefore, controlling the electrode placement by the patient’s perception of paresthesia distribution at perioperative stimulation is of high importance for a satisfactory result. Although the implantation of percutaneous electrodes has the advantage of a minimal invasive procedure which can be performed by most pain specialists, plate electrodes are generally less liable to dislocation, due to their larger size and their fixation to nearby tissue.

2.3. Targets of SCS

Both percutaneous and plate electrodes are placed medially in the dorsal epidural space opposite the *dorsal columns* (DCs) with the contact array(s) parallel to the spinal cord. The DCs include the ascending A β -fibers which are the targets to be stimulated. Apart from DC fibers, *dorsal root* (DR) fibers are stimulated as well. Stimulation of DRs, however, not only elicits (segmental) paresthesia but, at a slightly higher stimulation voltage, uncomfortable sensations and reflex muscle contractions as well. The latter stimulation voltage is the *discomfort threshold* and the upper limit of the *therapeutic range* of amplitudes which starts at the *perception threshold* of paresthesia. An extensive paresthesia coverage corresponding to a large pain area can only be obtained when the therapeutic range is sufficiently large. To increase the therapeutic range the threshold for DR stimulation should exceed the threshold for DC stimulation. The main factors affecting this threshold ratio (therapeutic range) are: (1) the anode-cathode separation on the epidural electrode and (2) the distance between the epidural electrode and the spinal cord. Generally, the therapeutic range and the extent of paresthesia coverage are increased when the anode-cathode separation gets smaller. Therefore, electrodes with a contact separation of 7 mm were introduced in addition to those with a 9 mm separation. The distance between the electrode and the spinal cord is strongly variable both among subjects, at different spinal levels of a subject and as a function of posture. This distance is smallest in the lower cervical region, larger in the low-thoracic region and largest in the mid-thoracic region. The large distance in the mid-thoracic region is responsible for the limited or lacking paresthesia when stimulating in this spinal region. Furthermore, the large anatomical variability is a main cause of the differences in paresthesia coverage and analgesia among subjects.

2.4. Cathode-anode combinations

The original contact spacing of a quadrupolar electrode (9-10 mm center-to-center) has been chosen to allow the selection of the optimum stimulation level (giving the “best” paresthesia coverage) within a spinal length corresponding to two vertebrae (30 mm) by using the appropriate contact as the cathode. In clinical practise, all 50 cathode-anode combinations are generally tested to select the “best” one, because small but clinically relevant differences in paresthesia coverage may exist. Theoretically, differences among combinations with the same contact as the cathode would be nonsignificant, because the distance between neighboring contacts is large (9-10 mm, or a multiple) as compared to the distance between a contact and the target (1-5 mm). Stimulation with any combination is therefore virtually unipolar and the stimulation field near a cathode will be hardly influenced by other cathode(s) and anode(s). The introduction of electrodes with a smaller contact spacing (7 mm) was an improvement, but is still far from the optimal value of 4-4.5 mm. It has been shown that a “narrow” bipole or tripole (guarded cathode) performs best.

Because single longitudinal quadrupolar arrays do not allow displacing the electric field mediolaterally, the use of dual percutaneous electrodes has been introduced in the nineties and was followed by the development of dual array plate electrodes. The two arrays should be placed symmetrically to the spinal cord (“physiological”) midline. These configurations, particularly those with offset contacts, allow the use of “narrow” bipoles and tripoles across the spinal cord midline. Although it has not been shown that dual electrodes perform better than single ones placed carefully over the spinal cord midline, their positions seem to be less critical, whereas another “best” contact combination can generally be found after electrode dislocation, thus avoiding electrode repositioning by surgical intervention.

2.5. Stimulation parameters

The *pulse amplitude*, e.g. the amplitude of the 1st phase of a biphasic pulse, may vary between a few tenths of a Volt and several Volts. This large variation is primarily related to the distance between the epidural electrode and the dorsal columns in the spinal cord (see 2.4). The *pulsewidth*, e.g. the duration of the 1st phase is generally between 150 and 500 μ s. Because it has been suggested that power consumption is least when the pulsewidth is 210 μ s, this value is generally used. Some clinicians have reported an increase of paresthesia coverage when the pulsewidth is increased. To minimize the neurophysiological effect of the 2nd phase of the charge-balanced pulse its amplitude is small, whereas its duration is much larger than the corresponding value of the 1st phase. The *pulse rate* giving most pain relief varies among subjects from 30/s to 80/s and may, according to some clinicians, even be as high as 250/s. Additional features in programming the pulse generator include the duration of on and off periods and a gradual increase and decrease in amplitude at the start and the end of a stimulation period, respectively. Moreover, the patient may select a stimulation amplitude from a few preset values when changing posture, and can put the stimulator on and off.

2.6. Concluding remarks

- The efficacy of SCS in chronic pain management is not evidence based in a methodological sense because of the paucity of prospective, randomized studies. Nevertheless, it has been shown to be successful over several years in a mean of 60% of the pain patients, where “successful” is defined as a pain relief of at least 50%. Factors limiting the efficacy are e.g. the various origins of the pain (see 1), the patient’s spinal anatomy (see 2.3), the geometry of the electrode(s) (see 2.4) and the often limited experience of clinicians with SCS procedures.
- In patients with chronic, neuropathic pain a limited stimulation session (e.g. 30 minutes) is generally followed by poststimulatory analgesia lasting up to 1-2 hours. This effect is a good indication of the effectiveness of the treatment.
- Not all dermatomes can easily be captured by SCS. Areas which are hard to cover with paresthesia include most parts of the trunk. Therefore, it is particularly difficult to relieve common chronic pain syndromes such as low-back pain and pelvic pain.
- An alternative approach to target the sacral dermatomes has recently been introduced. By this method a percutaneous electrode is positioned laterally in the lumbo-sacral epidural space in the vicinity of the sacral spinal nerve to be stimulated.
- The analgesic effect is generally established by the (subjective) visual analogue scale (VAS) rating, although measurement techniques by e.g. brain imaging (functional MRI) and electroencephalography are now available as well.
- There is still a lack of thorough understanding of the neurophysiological and neurochemical mechanisms underlying the analgesic effect of SCS. An improved knowledge of its mode(s) of action would most likely advance the efficacy of SCS.

- Other syndromes treated by SCS are peripheral vascular disease (PVD) and angina pectoris. Both vascular diseases are accompanied by ischemic pain and its relief is conceivably secondary to the stimulation-induced vasodilatation.

3. Peripheral Nerve Stimulation

Generally, SCS hardware is applied in PNS. Both types of SCS electrodes are used: quadrupolar plate electrodes are implanted beneath a nerve and proximal to the pain area, whereas percutaneous electrodes are placed inside a nerve via a small incision in the epineural sheath and are pushed distally to a favorable position. Stimulation parameters are similar to those used in SCS. The peripheral nerves most commonly stimulated with PNS are the ulnar, median, radial, tibial and peroneal nerves. Depending on the site of stimulation of these nerves paresthesia and analgesia can be elicited in the pain area. In contrast to SCS this method can only be applied in chronic, neuropathic pain syndromes covering a limited limb area, e.g. in causalgia. Due to limb movements electrode dislocation is a problem. Unless SCS, PNS is only used incidentally, and only few (non-controlled) studies have been published.

4. Transcutaneous Electrical Stimulation

When using TENS, a limb nerve is stimulated with skin electrodes. Except for the larger stimulus amplitude needed in transcutaneous stimulation, the stimulation parameters have the same values as in PNS and the effects are similar. It is likely that the same type of primary, cutaneous nerve fibers is stimulated with both SCS, PNS and TENS and that they all underly the “gate-control” and endorphin release mechanisms, because paresthesia and analgesia may be elicited instantaneously by all three techniques. In contrast to PNS, TENS is widely used by primarily physical therapists in the treatment of a variety of pain syndromes including chronic, neuropathic limb and low back pain. The results reported in the literature are mixed. Research studies have varied in the type of patients studied; the stimulation parameters employed; the placement of skin electrodes and the stimulation protocols.

Apart from conventional TENS, a second method is referred to as “acupuncture-like” TENS, by which a pulse rate below 10/s and a “higher” amplitude are used to stimulate for 15 or 30 seconds over pre-selected acupuncture points. The mechanism underlying this method is probably different, because it has an induction time for analgesia of 20-30 minutes. In TENS studies both methods often been employed. For a health technology that has come into widespread use, TENS has not undergone the necessary, extensive clinical evaluation by randomized, controlled trials to test for which pain conditions it would be an effective treatment.

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See:

- General Considerations in the Clinical Application of Electrical Stimulation
- References:
 - Comfort in Electrical Stimulation
 - Electrical Stimulation in Pain Modulation