Ann Agric Environ Med. 2013; Special Issue 1: 14–17
www.aaem.pl

REVIEW ARTICLE

The role of neurostimulation in the treatment of neuropathic pain

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Papuć E, Rejdak K. The role of neurostimulation in the treatment of neuropathic pain. Ann Agric Environ Med. 2013; Special Issue 1: 14–17.

Abstract

The treatment of chronic pain syndromes may include pharmacological, physiotherapeutic, and invasive methods. Considerable number of patients do not achieve sufficient pain relief with pharmacotherapy, in these patients with neuropathic pain, electrical neurostimulation may be applied. The available neurostimulation techniques which may be offered to the patients are: transcutaneous electrical nerve stimulation (TENS), peripheral nerve stimulation (PNS), nerve root stimulation (NRS), spinal cord stimulation (SCS), deep brain stimulation (DBS), epidural motor cortex stimulation (MCS), and repetitive transcranial magnetic stimulation (rTMS). These techniques vary in their invasiveness, stimulated structures and rationale, but they are all modifiable and reversible. Neurostimulation therapy is also used in addition to the current medical treatment in different neurological disorders, including Parkinson's disease, dystonia, obsessive-compulsive disorder, refractory pain, epilepsy and migraine. The article provides the physicians the knowledge on different neurostimulation techniques for treatment of chronic neuropathic pain and their effectiveness.

Key words

neurophatic pain, neurostimulation therapy, deep brain stimulation, transcranial magnetic stimulation, spinal cord stimulation, transcutaneous electrical nerve stimulation

INTRODUCTION

Pharmacological relief of neuropathic pain may be sometimes insufficient, thus electrical neurostimulation may be applied in chronic neuropathic pain and other neurological disorders. Certain number of patients do not achieve sufficient pain relief only with medication. In evidence-based studies on pain, the responders to treatment are those patients who report a pain relief at least 50%. On average 30–40% of the patients with chronic neuropathic pain achieve that target with pharmacotherapy [1, 2]. In placebo-controlled trials a significant reduction of chronic pain is defined as a two-point decrease or 30% reduction on a 0–10 numerical rating scale [3]. In addition pharmacological treatment, physical and psychological therapies may be often used. Although they may be helpful in relieving the pain, this may be often not sufficient for the patients with severe pain. Additionally, a number of surgical procedures may be also offered which alleviate neuropathic pain. Some of surgical lesion procedures are no longer performed, but as a substitute for this methods neurostimulation therapy has been introduced and is increasingly used. It may be also used in addition to the current medical treatment in different neurological conditions, including Parkinson's disease, dystonia, obsessive-compulsive disorder, refractory pain, epilepsy and migraine. The neurostimulation techniques proposed for treating pain are: transcutaneous electrical nerve stimulation (TENS), peripheral nerve stimulation (PNS), nerve root stimulation (NRS), spinal cord stimulation (SCS), deep brain stimulation (DBS), epidural motor cortex stimulation (MCS), and repetitive transcranial magnetic stimulation (rTMS). These techniques vary greatly in their degree of invasiveness, stimulated structures and effectiveness, but they are all reversible.

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Received: 29 October 2013; accepted: 29 December 2013

Peripheral stimulation. Peripheral stimulation comprises transcutaneous electrical nerve stimulation (TENS), peripheral nerve stimulation (PNS) and nerve root stimulation (NRS). TENS is the best known technique. In this procedure surface electrodes are located over the painful area or the nerve that innervates it and the stimulation is delivered at high frequency and low intensity (below pain threshold), to produce an intense activation of Aß afferent fibers and to evoke paresthesiae that cover the painful area. Different approach with the use of low-frequency and high-intensity stimuli that do elicit painful sensations may be also applied (this technique is also called acupuncture-like). In both situations, stimulation sessions of duration between 20–30 minutes are repeated at variable intervals. Because the pain relief is immediate but short lasting, many patients have the need to use a portable stimulator.

PNS is used when a more stable effect is desirable. In this procedure, electrodes are percutaneously implanted to contact directly the nerve (e.g. the main limb nerves, branches of the trigeminal or occipital nerves).

NRS is applied to cover the painful areas that are not accessible from the surface, such as pelvic viscera. A lead for stimulation is implanted deeply at the nerve root exit from the spine or into Meckel's cave to stimulate the Gasserian ganglion.

For all the above techniques, the probable mechanism of action, for the current of high frequency and low intensity, is inhibition exerted by large-size afferents on spinothalamic pathways. It is important to know that this inhibition is strictly homotopical (i.e. the large-fibre input must generate paresthesiae covering the entire painful territory) and that pain relief rapidly declines after stimulation is stopped [6]. The less commonly used low frequency and high-intensity

stimulation (acupuncture-like) is thought to activate, the antinociceptive systems; because it is at least partly naloxone-reversible, the analgesic effect is thought to be mediated by the opioid system [4, 5].

For application of TENS, pain must be confined to a relatively small area or a territory that is innervated by an easily accessible nerve. Another important condition is the sparing of Aß-fibres: patients with severe loss of such fibres (which may be easily assessed by the TENS evoked sensation) are unsuitable. Additionally, as transcutaneous stimulations are harmless, TENS may be often used as an adjunctive therapy to the drug or other physical treatments. Contrary to this, PNS/NRS have are used in pharmacoresistant patients [6].

It is difficult to assess effectiveness of all these methods, as data from randomized controlled studies are not comparable and results vary significantly between studies. The only conclusion is that the pain-relieving effect of TENS increases with dose (duration of the session, frequency of sessions and total duration). Standard high-frequency TENS is possibly better than placebo though probably worse than acupuncture-like or any other kind of electrical stimulation [6]. It is difficult to make conclusions for PNS and NRS as data from randomized controlled studies are lacking.

Spinal cord stimulation (SCS). The technique consists of implantation of electrodes into the posterior epidural space of the thoracic or cervical spine ipsilaterally to the pain (if unilateral) and at an appropriate level to evoke paraesthesiae which are a pre-requisite condition for success. Catheter or wire electrodes can be inserted percutaneously under local or general anaesthesia; plate electrode systems require an open operation but may be more effective. The method requires implantation of a pulse generator (IPG).

SCS can modulate different elements of neuropathic pain, including allodynia and additionally it has also an anti-ischaemic action, both cardiac and in the periphery, and other autonomic effects including the normalization of the autonomic manifestations of complex regional pain syndromes. The effect of SCS is mediated by large-myelinated Aß afferents, whose collaterals ascend in the dorsal columns.

SCS may be effective against various ischaemic and specific neuropathic pain syndromes. Trial stimulation via externalized leads is commonly used: it may help to identify the patients who do not like the sensation from SCS and those in whom appropriate effects cannot be achieved.

One of the randomized controlled studies on failed back surgery syndrome revealed that SCS is more effective than reoperation [7] and others [8, 9] showed that its addition is more effective than conventional medical care alone.

In randomized controlled trials [6], the responders (pain relief >50%) to SCS were 47–48% in the treated group versus 9–12% in the controls, the observational period being of 6–24 months. In complex regional pain syndrome (CRPS) type I, results and evidence level are also good, with a single randomized controlled study of SCS compared with conventional care alone [10].

Deep brain stimulation. Deep brain stimulation may be applied for the treatment of medically refractory chronic pain. Deep brain targets include the sensory part of thalamus (ventral posterior lateral, VPL) and periventricular gray matter (PVG) as well as periaqueductal gray matter (PAG) contralateral to the pain if unilateral, or bilaterally if indicated. Both locations have been targets in the treatment of pain with DBS for three decades [11, 12].

For target localization brain MRI, stereotactic computerized tomography and brain atlas are used. An electrode is stereotactically inserted into subcortical brain structures under local anesthesia. The electrodes are connected to a subcutaneous IPG, placed in the chest.

Patients usually have electrodes implanted to both VPL and PVG to later undergo a test trial stimulation period for a few days, while receiving antibiotic treatment. Double-blinded test stimulation is recommended after electrodes implantation. Each lead should be tested separately and later in combination, after this the optimal electrode contacts are determined [13]. After determination of the threshold for experiencing any stimulation-induced effects (like paresthesias during stimulation of somatosensory thalamus; floating, dizziness, and/or panic in PVG), testing is conducted with subthreshold stimulation (0.5–1 V below threshold), half of the intensity of subthreshold stimulation, and placebo stimulation (intensity set tozero). The patient as well as the evaluating physician asses the pain relief on the VAS score, being unaware of the stimulator settings. Based on the results of this trial stimulation, the decision is made to proceed with permanent implantation (internalization) of the IPG.

Because of its invasiveness and the risks associated with DBS, it is restricted to a selected group of patients in whom conservative treatment of chronic pain syndromes has been ineffective. The technique of DBS has been used since the 1950s, nevertheless it should be treated a last-chance therapy in patients in whom all the less invasive procedures have failed, as it carries a small but serious risk of intracranial hemorrhage (1–5%) [14]. In general, combined stimulation of PVG and VPL has better effects single-lead stimulation [13].

Candidates for DBS are patients with peripheral neuropathic pain, trigeminal neuropathic pain and/or dysesthesia dolorosa, phantom-limb pain and central pain syndromes. The results in patients with central pain syndromes are however not favorable. Moderate results were observed in patients with the thalamic pain syndrome or poststroke chronic central pain [13]. Although some beneficial effects on allodynia after PVG stimulation was observed, this did not significantly influenced the patients' quality of life because of the persistent chronic burning pain component [13]. In some patients poor results of trial stimulation do not even satisfy the criteria for internalization of the electrodes, which are removed after unsuccessful trial. Patient selection is very important, additionally to identification of patients who would benefit from DBS most, trial stimulation is performed [15]. Nevertheless, successful trial stimulation does not result in long-term success in up to half of patients. Patients with long-lasting postherpetic neuralgia are poor responders due to central changes within the spinal cord or even more central sites [13].

The mechanisms of pain relieving action of DBS remains unclear. Animal studies have shown that thalamic stimulation suppresses deafferentation pain, probably via thalamo-corticofugal descending pathways [EFNS guidelines]. Presently it is believed that stimulation of ventral PVG engages nonopioid dependent analgesia pathways, whereas stimulation of dorsal PVG involves opioid-related analgesia with associated autonomic effects [16].

What is interesting, lower frequencies (5–50 Hz) have analgesic, whereas higher frequencies (>70 Hz) pain-provoking effect.

Results of one meta-analysis [17], revealed that DBS is more effective for nociceptive pain than for neuropathic pain (63% vs. 47% long-term success). In patients with neuropathic pain, better results were observed in patients with peripheral lesions (radiculopathies, plexopathies and neuropathies) [17].

Two studies regarding stimulation of the somatosensory thalamus or PAG/PVG, were published so far: one study performed in 15 patients with central post-stroke pain (CPSP), considered DBS successful (pain relief >30%) in 67% of patients at long-term [15]; the other, in 21 patients with various neuropathic pain conditions, concluded that DBS had low efficacy, with only 24% of patients maintaining long-term benefit (i.e. they were willing to keep using DBS after 5 years) none of these patients having CPSP [18]. To conclude DBS should be performed in experienced, specialized centres, using established outcome measures.

Medical treatment options should be exhausted before patients are considered for brain stimulation. A careful patient history should be taken to rule out inefficient dosages or side effects. Especially patients with neuropathic pain should be treated for a sufficient amount of time with tricyclic antidepressants (amitriptyline), anticonvulsants (carbamazepine, gabapentin, pregabalin), and other medications (mexiletine, baclofen) before DBS is performed. Additionally, pain of peripheral origin should be treated first with SCS or peripheral nerve stimulation, if possible [13].

Patients should be treated in a multidisciplinary pain clinic before being referred for DBS, and finally, psychiatric and psychological testing should be conducted before considering a patient for DBS implantation. According to the results in this study, DBS can be helpful and add to the quality of life in carefully selected patients with chronic pain syndromes.

Motor cortex stimulation. In this method epidural electrodes are implanted over the central brain area through the frontoparietal craniotomy. One or two electrodes are implanted over the motor representation of the painful area, either parallel or orthogonal to the central sulcus. The electrode is connected to a subcutaneous IPG. The stimulation parameters are adjusted post-operatively, keeping the intensity below motor threshold, and the stimulation is usually put on cyclic mode (alternating on and off periods). The mechanism of action of MCS remains unknown. There is some evidence that MTS does not significantly activate sensory-motor cortex, whilst a strong focal activation may be observed in thalamus, insula, cingulate-orbitofrontal junction and brainstem [19], suggesting that MCS-induced pain relief may relate to down activation of descending pain control systems going from motorcortex to thalamus, and perhaps to motor brainstem nuclei as well as to blunting of affective reactions to pain via activation of orbitofrontal-perigenual cingulate cortex [20].

The fact that many of the regions activated by MCS contain high levels of opioid receptors suggests that long-lasting MCS effects may also involve secretion of endogenous opioids.

MCT may be connected with some undesired events related to malfunction of the stimulating apparatus (e.g. unexpected battery depletion). Seizures, wound infection, sepsis, extradural haematoma, and pain induced by MCS have been occasionally reported. Overall 20% of patients experience one or more complications, usually of benign nature.

Repetitive transcranial magnetic stimulation. The aim of rTMS in patients with chronic pain aims is analgesic effects by means of a non-invasive cortical stimulation [21]. The stimulation is performed by applying on the scalp, above a targeted cortical region, the coil of a magnetic stimulator.

The frequency and the total number of delivered pulses is variable. One single session should last at least 20 min and should include at least 1000 pulses. Daily sessions can be repeated for one or several weeks. There is no induced pain and no need for anesthesia or for hospital stay during the treatment.

The rationale to use rTMS is the same as for MCS. The stimulation is thought to activate some fibres that run through the motor cortex and project to remote structures involved in some aspects of neuropathic pain processing (emotional or sensori-discriminative components). The greatest advantage is that the method is non-invasive and can be applied to any patient with drug-resistant, chronic neuropathic pain, who could be candidate for the implantation of a cortical stimulator. As the clinical effects are rather moderate and short-lasting beyond the time of a single session of stimulation, this method should not be considered a therapeutic method but rather diagnostic method, except if the sessions of stimulation are repeated for several days or weeks. Because the effect is modest and short-lasting, rTMS should not be used as the sole treatment in chronic neuropathic pain. It may be proposed for short lasting pains or to identify suitable candidates for an epidural implant (MCS).

CONCLUSIONS

Peripheral stimulations have been rarely used in neuropathic pain. Unlike other neurostimulation procedures, TENS is easy to be applied and devoid of any risk. This is why TENS is so widely used in acute and chronic pain patients. Spinal cord stimulation, DBS and MCS are typically used when all other treatments have failed. Although DBS is not a new therapy, it has changed considerably over the last decade, together with advances in both stimulator technology and neuroimaging techniques, leading to improved efficacy and reduced number of complications. Nevertheless, DBS should be performed in experienced, specialist centers. DBS appears to be a promising for phantom limb pain and trigeminal neuropathic pains. Motor cortex stimulation is applicable in central or peripheral facial pain. Interestingly, the best results are observed for patients with facial pain relative to all other pain types. Similarly to TENS, the efficacy of rTMS seems to increase with dose: higher frequency, longer duration of the session, and more sessions tend to improve the results. Because its clinical effects are rather modest and short-lasting, rTMS cannot be considered as a long term therapeutic method. It can be rather proposed as a non-invasive pre-operative therapeutic test for patients with drug resistant chronic pain who are candidates for chronic MCS.

Concerning side effects, TENS and rTMS are almost devoid of side-effects. SCS, DBS and MCS may be associated with adverse events in a large proportion of patients (up to 20% with MCS and 40% with SCS experience one or more complications) [EFNS]. However, most of these are mild, like lead migration or battery depletion that can usually be solved. Real harms are few, usually wound infection (3.4%

with SCS, 7.3% with DBS and 2.2% with MCS) and in very rare cases: aseptic meningitis, transient paraparesis, epidural hematoma, epileptic seizures and skin reactions.

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