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Neuromodulation techniques for treatment of refractory neuropathic pain

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Introduction

Electrical neuromodulation techique is used for treatment of chronic neuropathic pain refractory to drug therapy with painkillers or anticonvulsivant. It generally involves the selective application of a programmable pulse waveform through a series of electrode within a lead to stimulate afferent nerve fibers, spinal dorsal columns, deep brain regions or cortical brain areas. The pulse wave is generated by an implantable pulse generator that contain a battery pack and a electronic module allowing external programming. The use of an external trial stimulation period to assess the potential response prior to definitive programmed pulse generator implantation is widespread but not universally used. Trough the initial costs may be high, electrical neuromodulation techniques have proven to be cost effective in the long term. Careful selection of patients, a thorough understanding of anatomy, neurophysiology and pharmacology and expertise in performance of these procedures are vital for success (1).

The stimulation techniques used till today are: Peripheral Nerve Stimulation (PNS), Peripheral Nerve Field Stimulation (PNFS), Spinal Cord Stimulation (SCS), Deep Brain Stimulation (DBS) and Motor Cortex Stimulation (MCS).

Each of these stimulation had specific indications related to the type of neuropathic pain condition.

Peripheral Nerve Stimulation

PNS is an excellent modality of treatment of various neuropathic pain conditions alone or in association with other electrical neuromodulation procedures like SCS and DBS. Pain limited to a particular nerve distribution is likely to respond to PNS (2).

The approach of lead implant may include either direct exposure of the nerve with cylindrical or paddle lead implanted next to it or wrapped around it, or percutaneous lead implant through a needle inserted perpendicular to the nerve course or along its course.

As with SCS, it is customary to subject the patient to trial stimulation to assess response prior to permanent electrode and IPG implant.

PNS is recommended for trigeminal neuropathic pain in infraorbital and supraorbital distribution, inguinal pain in post-herniorrhaphy pain syndromes, post-traumatic and post-surgical neuropathies, complex regional pain syndromes, postherpetic neuralgia, coccygodynia.

Emerging indications are cluster headaches, chronic daily headaches, classic migraine, transformed migraine presenting with occipital pain and discomfort, hemicrania continua, isolated pelvic pain or pelvic pain associated with lower urinary tract or bowel dysfunctions.

The mechanism of action of PNS is still largely unknown: direct excitation of central pain processing systems, direct blocking of painfull afferents direct at the nerve.

Peripheral Nerve Field Stimulation

PNFS is recently introduced in clinical practice and provides an exciting new frontier in pain management. It is based on the assumption that subdermal application of an electric filed can interfere with the transmission of pain, thus decreasing the local sensation of pain.

The main indications for the use of this therapy are hard to stimulate areas with other stimulation modalities and well defined areas of pain. Therefore PNFS can be proposed for patients with pain in axial, paravertebral, scapular and groin areas where spinal cord stimulation do not provide a consistent paresthesia coverage, and for patients with painful scars with nerve entrapment (3).
One or more cylindrical leads are implanted vertically, horizontally or sideways into subcutaneous tissue in the epifascial plane within the area of maximum pain through 15-gauge Tuohy needle. The electrode array length is important for maximum coverage. One eight-electrode lead offers an electrode array of 66

mm while a single four-electrode offers an electrode array of 60 mm.

As for all neurostimulation procedures, it is customary to subject the patient to trial stimulation to asses response prior to permanent lead and IPG implant. Possible complications are: lead dislodgment and slinding away from the initial determined site, skin erosion over the lead.

The mechanism of action of PNFS continues to be investigated. Neuromodulating effects may be due to stimulation of large diameter A-Beta fibers that modulates afferent output of smaller A-delta and C fibers ("gate-control theory"). Other theories include local stimulation of nerve endings in the skin, local antinflammatory and membrane depolarizing effect, or a central action via anterograde activation of A-beta nerve fibres.

Spinal Cord Stimulation

SCS has been part of the neurosurgeon's armamentarium for severals years. SCS is more effective in neuropathic pain by peripheral genesis than in those by central origin: in particular it is active on radicular pain, from inflammatory of the nervous tissue and from peripheral nervous lesion, provided that there is not a complete deafferentation. Clinical conditions which represent widely accepted indication for SCS include Failed Back Surgery Syndrome (FBSS) and Complex Regional Pain Syndrome (CRPS). The majority of FBSS patients and around 50% to 60% of CPRS patients treated with SCS report at least a 50% reduction in pain as well as functional improvement (5).

Leads used for implant are of two types, quadripolar/octopolar cylindrical leads and quadripolar/ octopolar/multipolar paddle leads. According to lead type the implant is performed with different techniques: percutaneous technique and surgical technique. In the percutaneous technique one or two cylindrical leads are implanted under fluoroscopy control through a Tuohy needle and with local anaesthesia: it is therefore possible to verify the correct positioning by the evocation of appropriate paresthesia field covering patient's pain irradiation zone (at least 80% of this area).

In the surgical technique a paddle lead is implanted under direct vision with a partial laminotomy/laminectomy performed under general anaesthesia or, less frequently, under spinal or local anaesthesia: only if the last two types of anaesthesia are used it is possible to evoke intraoperative paresthesia (4). The use of an external trial stimulation period to asses the potential response prior to definitive programmed pulse generator implantation is widespread but not universally used.

Concerning the mechanism of action several theory are proposed: orthodromically activation of A-Beta fibres with stimulation of supraspinal modulation centers of brainstem and of inhibitory descending pathways; antidromically activation of A-Beta fibres and its collaterals with stimulation of interneurons responsible for inhibition of primary nocicettive A-delta and C afferent fibres ("gates control"); block of transmission in A-delta and C fibres for collision; increase release of inhibitory neurotransmitters in cerebrospinal fluid (GABA, Serotonin, Substance P, Glicina).

Deep Brain Stimulation

DBS for neuropathic pain syndromes was one of the earliest indications for neuromodulation but, despite the apparent successes rate, the technique was abandoned up to the 2000 when it was revalued.

Till today the procedure employed for high frequency stimulation of deep brain regions are: DBS of VPL-PVG/PAG and DBS of hypothalamus.

Stereotactic lead implantation in sensory thalamus (VPL) and peri-ventricular and peri-aqueductal grey area (PVG/PAG) contro-lateral to the side of pain is used for treatment of phantom limb pain, postherpetic neuralgia, anaesthesia dolorosa, brachial plexus injury and neuropathic pain secondary to neural damage from variety of causes with satisfactory results in about 60%-65% of cases. However the outcomes of surgery appear to vary according to aetiology (7). Hypothalamic stimulation involves the bilateral stereotactic implantation of leads into the posteromedial hypothalamus (8).

Electrical stimulation of this target may restore hypothalamic modulation of the caudal trigeminal nucleus, thus preventing activation of the trigeminofacial reflex thought to be responsible for the pain and autonomic phenomena in Trigeminal Autonomic Cephalalgias (TACs) (9): those are a grouping of headache syndromes that includes chronic cluster headache, paroxysmal hemicrania and short

lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). Results are very satisfactory mainly in cluster headache and SUNCT. The procedure also seems acceptably safe: anyway because possible cerebral hemorrhagic complications can be a life-threatening occurrence, hypothalamic implantation should only be considered as a last resort in TACs patients who do not respond to extensive trials of all available conservative treatments (10).

Motor Cortex Stimulation

The potential candidates for MCS are patient with a history of neuropathic pain mainly of trigeminal or central origin and a failure of the proper pharmacological management. The most common pain type treated is post-stroke pain followed by trigeminal-neuropathic pain; peripheral nerve injury pain, spinal cord injury pain, brachial plexus avulsion pain and phantom-limb pain are also reported in literature. The pain control (>50% of pain reduction) ranges from 40% to 75% with best results in trigeminal pain (6).

Technically, MCS involves the implantation of a epidural paddle lead by a burr hole or a small craniotomy over the Motor Cortex contro-lateral to the side of pain. Primary Motor Cortex can be localized by either radiological landmarks of the central sulcus, intraoperative somatosensory evoked potential (SSEP) with observation of “N20/P20 phase reversal” over the central sulcus, intraoperative stimulation of the cortex with seizure threshold and use of neuronavigation systems.

The action mechanism remains poorly understood. MCS reduces the hyperactivity of thalamic neurones and the hyperactivity at dorsal columns nuclei: descending inhibitory mechanism at spinal level may be involved in mediating the effect of stimulation. Besides MCS may also reduce the emotional component of chronic pain by activating anterior cingulated cortex and anterior insula.

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