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NEUROSURGICAL INTERVENTIONS FOR THE MANAGEMENT OF NEUROPATHIC PAIN: A REVIEW OF CURRENT EVIDENCE

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Abstract: To analyze and describe available neurosurgical interventions for the management of neuropathic pain, evaluating the efficacy, safety, indications, risks and benefits of different neurosurgical approaches, with a focus on neuromodulation techniques and other neuroablative procedures. Methodology: Narrative bibliographic review between April and May 2023, using the PubMed Central (PMC) database through pre-selected descriptors in different combinations. After applying inclusion and exclusion criteria, 16 studies were selected for analysis. **Results**: Neuropathic pain presents a challenge in its management, often being refractory to available therapeutic interventions, affecting 10% of the global population, highlighting the importance of an accurate assessment for choosing therapies with better prognosis for patients. Surgical therapy, reserved for refractory cases, is divided into ablative procedures and neuromodulation. Ablative surgery seeks permanent inactivation of pain pathways or nerve roots, including procedures such as thalamotomy, neurotomy, cordotomy, rhizotomy, among others. **Final Considerations**: Neuromodulation has stood out as a relevant approach in the surgical arsenal for chronic pain, offering reversible and testable methods, including pharmacological or electrical approaches, through invasive or non-invasive techniques.

Keywords: Pain Surgery, Neuromodulation, Neuropathic Pain, Neurosurgical Treatment.

INTRODUCTION

Chronic pain, persistent for more than six months, is categorized as nociceptive, neuropathic or oncological (MOISSET X. et al., 2019). Nociceptive pain is linked to the activation of peripheral pain receptors, while neuropathic pain, affecting about 7-10% of the global population, mainly those over 50 years of age, results from an injury to the

Somatosensory Nervous System (BURCHIEL K.J; AHMED M.R., 2019). The latter has several subtypes, including chronic peripheral and central neuropathic pain, with cancer pain resulting from malignant pathologies causing damage to the nervous system and tissues (BURCHIEL K.J; AHMED M.R., 2019).

The treatment of neuropathic pain, challenging due to the absence of specific drugs and the high incidence of significant side effects, includes pharmacological and non-pharmacological interventions (GALHORDONI R. et al., 2019; BURCHIEL K.J; AHMED M.R., 2019). Surgical therapy is divided between ablative procedures and neuromodulation. The latter have received more attention, allowing the manipulation of electrical and neurochemical signaling of pain detection and reaction systems (TEXAKALIDIS P. et al., 2019.).

In recent decades, ablative procedures have been replaced by the concept of neuromodulation, which includes reversible and testable methods. The approach involves manipulating the electrical and neurochemical signaling of pain detection and reaction systems. Neuromodulation leads the surgical arsenal for controlling chronic pain not resulting from malignancy through pharmacological neuromodulatory approaches, such as the use of intrathecal pumps to administer drugs into the cerebrospinal fluid space, or electrical approaches, using electrical stimuli that modulate various nervous system targets such as brain, spinal cord, peripheral nerves and dorsal root ganglia (GALHORDONI R. et al., 2019).

Faced with this scenario, the objective of this narrative review is to analyze the neurosurgical interventions currently available for the management of neuropathic pain, evaluating their effectiveness, indications, risks and benefits. The review will seek to examine recent clinical trials, systematic reviews, and meta-analyses that investigate the efficacy and safety of different neurosurgical approaches with a focus on neuromodulation techniques and other types of neuroablative procedures. Furthermore, we discuss the clinical and practical implications of these interventions, identify gaps in the current literature, and highlight areas for future research in the field of neurosurgery to improve understanding and management of refractory neuropathic pain.

METHODOLOGY

This is a bibliographic review developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. Used for the research elaboration through its guiding question: "What are the neurosurgical interventions currently available for the management of refractory neuropathic pain and how effective are these approaches in relation to the improvement of clinical results and the quality of life of patients?". The searches were carried out through searches in the PubMed Central (PMC) database. Descriptors were used in different combinations with the Boolean term "AND": Pain surgery/Cirurgia da dor; Neuromodulation/Neuromodulation; Neuromodulation surgical techniques/ Neuromodulation surgical techniques; Neuropathic pain/Neuropathic pain; Neurosurgical treatment/Neurosurgical treatment. From this search, 273 articles were found, subsequently submitted to the selection criteria. Inclusion criteria were: articles in English; published from 2018 to 2023 and addressed the themes proposed for this research, review-type studies; cientific magazine; systematic review; literature review; randomized clinical trials and cohort studies, available in full. Exclusion criteria were: duplicate articles, available in summary form, which did not directly address the studied proposal and which did not meet the other inclusion criteria. After applying the inclusion and exclusion criteria, 16 studies were selected to compose the collection.

RESULTS

Neuropathic pain is a management challenge, often refractory to available therapeutic interventions. Studies indicate that this condition affects up to 10% of the global population, reinforcing the importance of an accurate assessment and diagnosis of the painful condition, so that therapies capable of offering the best prognosis to the patient are chosen (ATTAL N., et al, 2021; FELIX E.R., 2014). For the most part, neuropathic pain treatment focuses on symptom control, with pharmacological interventions being considered the first-line strategy (OLIVEIRA R.A.A. et al., 2020). However, therapeutic management is challenging in clinical practice, and concerns have recently been reported about the misuse and safety of the first-line drugs, pregabalin and gabapentin (ATTAL N., et al, 2021).

Among the classes of drugs used for pain management, antidepressants, anticonvulsants and opioid analgesics stand out. Tricyclic antidepressants inhibit serotonin and noradrenaline reuptake in presynaptic terminals, potentiating the descending inhibitory pathway. Anticonvulsants work by preventing excessive neuronal firing, a common feature in epileptic disorders and chronic neuropathic pain. Opioids, on the other hand, inhibit the release of local excitatory neurotransmitters, such as glutamate and substance P, reducing the sensation of pain (SZOK D. et al., 2019). However, drug therapy has limited efficacy and is strongly associated with the occurrence of iatrogenic effects. In this context, non-pharmacological alternative therapies, such as physiotherapy, acupuncture and psychotherapy, have gained prominence (OLIVEIRA R.A.A. et al., 2020).

A significant portion of patients do not respond adequately to conventional pharmacological approaches. For these refractory cases, surgical and neuromodulatory interventions have been widely explored (HAMANI C., et al, 2021; GATZINSKY K., et al, 2021). In recent years, new approaches based on non-invasive brain stimulation, such as repetitive transcranial magnetic stimulation (rTMS), have been proposed (ATTAL N., et al, 2021). Surgical treatment of neuropathic pain can be divided into ablative and neuromodulation procedures. In the context of the treatment of refractory chronic neuropathic pain, rTMS and stimulation of the motor cortex through surgically implanted electrodes have shown therapeutic potential (HAMANI C., et al, 2021; GATZINSKY K., et al, 2021).

Currently, neuromodulation occupies a prominent position in the arsenal of surgeries for chronic pain (BURCHIEL K.J.; AHMED M.R., 2019). Current neuromodulatory approaches used for pain control are either pharmacological or electrical. The pharmacological technique uses intrathecal infusion pumps to administer medication directly into the CSF space, while the electrical technique uses electrodes to modulate the nervous system through the emission of adjustable electrical currents, inhibiting specific regions of the spinal cord and brain. In turn, ablative surgery aims to restore function through permanent inactivation of pain pathways or nerve roots, as occurs in thalamotomy, neurotomy, cordotomy, rhizotomy and mesencephalotomy (BURCHIEL K.J.; AHMED M.R., 2019).

Ideally, patients with neuropathic pain must first undergo minimally invasive procedures, such as neuromodulation and neurostimulation. More invasive therapies, such as ablative ones, must be reserved for refractory cases (TEXAKALIDIS P. et al., 2019). Among the methods of ablative surgery are: sympathectomy, cordotomy, myelotomy, mesencephalotomy, cingulotomy and dorsal root entry lesion (GILLER C.A., 2003). In contrast, neurostimulation-based procedures include therapies targeting the spinal cord and ganglia, in addition to cerebral, invasive, deep, and transcutaneous therapies. Non-invasive spinal cord and ganglia stimulation therapies are: spinal cord stimulation, high frequency stimulation and spinal cord dorsal root ganglion stimulation (GALAFASSI G.Z. et al., 2021; HAMANI C. et al, 2021; DEER T.R et al., 2020). Invasive techniques may include: electrical stimulation of the motor cortex, deep brain stimulation, and posterior insula stimulation (PARRAVANO D.C. et al., 2019; HAMANI C., et al, 2021; MOISSET X. et al., 2019; GALAFASSI G.Z. et al.., 2021). Finally, among non-invasive brain stimulation techniques are transcranial stimulation and transcutaneous electrical nerve stimulation (MOISSET X., et al, 2021; GALHARDONI R. et al., 2019; GATZINSKY K., et al, 2021).

The principle of ablative methods is the interruption of pain pathways through a controlled injury to the structure. This can be achieved through chemical, thermal, ischemic and actinic injuries (GILLER C.A., 2003). Simply put, sympathectomies are performed through injury to some sympathetic chains, and can be used to treat complex regional pain syndrome type 1 and type 2. It is best indicated when there is already improvement in pain after blocking the sympathetic chains with local anesthetics. Finally, its main complication is compensatory hyperhidrosis (GILLER C.A., 2003).

Cordotomy is described as injury to the spinothalamic tract, in the anterolateral region, on the side contralateral to the referred pain. The benefits are immediate, however it is used only for the treatment of cancer pain with a life expectancy of less than one year, since the results are rarely maintained after 2 years of the procedure. Cordotomy can be unilateral or bilateral. This has few indications, and may be a possibility in cases of bilateral abdominal, pelvic or extremity pain (GILLER C.A., 2003).

Myelotomy, on the other hand, is based on injury to the spinoreticulothalamic tract that crosses the midline. It is used to treat pelvi-perineal and lower limb cancer pain in patients in whom bilateral cordotomy is risky. It has also shown success when performed to treat painful spasticity after spinal cord injury (GILLER C.A., 2003).

Mesencephalotomy is aimed at interrupting the spinoreticulothalamic pathways involved in the paresthetic sensation typical of neuropathic pain. It can be used in cases of painful anesthesia of the face, post brachial plexus avulsion pain, phantom pain and post amputation stump pain. In these cases, the lesion is too high to perform a cordotomy or to inject anesthetic agents (GILLER C.A., 2003).

Focused on lesions in the cingulate gyrus, cingulotomy stands out, being widely used in the treatment of cancer pain. As the emotional component is the focus of treatment in this modality of procedure, the results are better in those patients who have psychiatric comorbidities (GILLER C.A., 2003).

The Dorsal Root Entry Zone Injury consists of performing approximately 60 lesions in the dorsal root entry zone. It is mainly indicated for the treatment of pain syndromes after cervical or lumbar root avulsion, in addition to being able to be used in the treatment of pain restricted to the lesion level after spinal cord trauma (GILLER C.A., 2003). The literature also presents data for its use in the treatment of postherpetic neuralgia. In a literature review that evaluated 6 studies on the subject, 26 out of 65 patients (40%) had their pain reduced by 50% and 14 out of 19 patients (73.7%) reduced or discontinued their pain control medications after procedure (GATZINSKY K. et al., 2021)

Spinal cord stimulation takes place by implanting generators connected to two electrodes that connect the posterior epidural space to the dorsal column of the spinal cord (GALAFASSI G.Z. et al., 2021). The mechanisms by which electrical stimulation improves neuropathic pain are still complex. However, it is apparently related to the activation of GABAergic inhibitory interneurons, with the decrease in the postsynaptic currents of the Aβ fibers, resulting from the blockade of the cannabinoid receptor 1 in the dorsal horn of the medulla and with the release of other neurotransmitters, such as opioids and acetylcholine. In addition, electrical stimulation can also act on the supraspinal systems, leading to descending inhibition through the release of neurotransmitters such as acetylcholine and noradrenaline, which in turn act by modulating wide dynamic range (WDR) neurons. in the posterior horn of the medulla (GALAFASSI G.Z. et al., 2021; HAMANI C. et al, 2021).

Electrical stimulation of the spinal cord is mainly indicated for the treatment of spinal surgery failure syndrome, complex regional pain syndrome, and neuropathic pain. Studies have shown the superiority of electrical stimulation compared to reoperation and conventional medical treatment with opioids, antiepileptics, antidepressants, nonsteroidal anti-inflammatory drugs, physical and psychological rehabilitation therapy, among others. However, such studies have weaknesses such as small population, cross design and industry support (DEER T.R et al., 2020).

The European Federation of Neurological Societies (EFNS) and the IASP Special Interest Group on Neuropathic Pain (NeuPSIG) have given electrical stimulation of the spinal cord a weak recommendation in the treatment of failed spinal surgery syndrome and complex regional pain syndrome. The European Academy of Neurology also gave this method a weak recommendation for the treatment of diabetic neuropathic pain (HAMANI C. et al, 2021). On the other hand, high-frequency stimulation is supported by the protocols of the National Institute for Health and Care Excellence (NICE) as potentially effective for the treatment of neuropathic and ischemic pain in groups of patients who do not have a risk factor for failure of the treatment (use of high doses of opioids, secondary gain and psychiatric comorbidities) (GALAFASSI G.Z. et al., 2021).

Finally, dorsal root ganglion stimulation is another form of neurostimulation and has been increasingly studied. It promotes preferential activation of primary sensory fibers, modifying the activity of inhibitory and excitatory interneurons in the dorsal horn of the spinal cord. This results in a decrease in the influx of nociceptive signals transmitted by Aδ and C fibers (DEER T.R et al., 2020). Indications of this technique include focal neuropathic pain in upper and lower limbs, chronic low back pain after lumbar surgery, complex regional pain syndrome, post amputation pain and trigeminal neuralgia (DEER T.R et al., 2020).

High-frequency stimulation therapy, which delivers high-frequency, low-amplitude, short-duration pulses, has demonstrated superiority over conventional electrical stimulation. Studies suggest that therapeutic benefits may extend not only to patients with radicular pain in the lower limbs, but also to those with low back pain (DEER T.R et al., 2020; GALAFASSI G.Z. et al., 2021).

Burst stimulation, which applies pulses of five consecutive waves to an internal point at a specific frequency and pulse width, 40 times per second, also had advantages over conventional electrical stimulation, as revealed by an industry-sponsored study (DEER T.R. et al., 2020; GALAFASSI G.Z. et al., 2021).

By placing an electrode on the dorsal root ganglion and stimulating this structure, one can block signaling from the primary sensory units, a technique known as spinal cord dorsal root ganglion stimulation. Often used in patients with dermatomal pain, mainly between T10 and S2, this approach has demonstrated efficacy, supported by moderate-level evidence, in reducing pain, especially in cases of focal neuropathic pain and complex regional pain syndrome (DEER T.R et al.., 2020; DEER T.R. et al., 2020a; GALAFASSI G.Z. et al., 2021).

Although motor cortex stimulation has been used for some time in the management of refractory neuropathic pain, its analgesic effects on improving quality of life are still not fully understood. thalamic nuclei responsible for pain perception, through the activation of descending pathways that originate in the cortex and end in the spinal cord. This technique involves a craniotomy for the implantation of electrodes in the motor cortex, generating electrical impulses in the region (PARRAVANO D.C. et al., 2019). The impact on quality of life in the studies varies between 35 and 85%. The lack of standardization of the technique and the diversity of diagnoses that culminate in neuropathic pain contribute to the heterogeneity of the studies. Notably, patients with complex regional pain syndrome, phantom limb pain, and facial neuropathic pain had better outcomes compared to those with neuropathic pain after stroke and brachial plexus avulsion. Research indicates that a substantial postoperative analgesic effect was observed after electrode insertion, even in the absence of stimulation. Individuals whose diagnoses are associated with good postoperative outcomes or who developed an insertional effect were almost 100% likely to respond to motor cortex stimulation (HAMANI C., et al, 2021).

Deep brain stimulation, a technique used to manage refractory chronic neuropathic pain, frequently used between the 1970s and 1980s, involves the implantation of electrodes in thalamic and deep regions of the gray matter, such as the periaqueductal and periventricular regions. This technique has been used to treat a variety of neurological conditions, including Parkinson's disease, essential tremor and dystonia, but its use for pain management is still an emerging field of study. Target structures for deep brain stimulation in pain management include the ventral posterior lateral thalamus, the periaqueductal gray nucleus, the reticular formation, and the anterior cingulate cortex (HAMANI C., et al, 2021; MOISSET X. et al., 2019). Although effective in reducing neuropathic pain, as demonstrated in a meta-analysis involving more than 400 patients, the technique is associated with complications such as intracranial hemorrhage and infection. Given the lack of strong evidence of its effectiveness and the existence of less invasive and dangerous methods, deep brain stimulation has been reserved for cases of chronic neuropathic pain where other therapeutic options have proven ineffective (MOISSET X. et al., 2019).

Among emerging techniques, posterior insula stimulation is a new approach, potentially usable in the future for the treatment of refractory neuropathic pain. This new modality of invasive neurostimulation that has shown encouraging preliminary results in the treatment of patients. The posterior insula is an area of the brain that has been implicated in pain perception, emotion regulation, and cognitive behavior. It is believed that stimulation of this area can help modulate pain perception (GALAFASSI G.Z. et al., 2021). However, the scarcity of studies on this technique currently prevents the assertion of its effectiveness for patients with neuropathic pain. Although the technique is supported by the scientific community for future trials, its routine use is not yet recommended (GALAFASSI G.Z. et al., 2021).

Among non-invasive brain neurostimulation techniques, transcranial direct current stimulation and transcranial magnetic stimulation have been explored as alternatives for the treatment of neuropathic pain. Both techniques have shown positive results in clinical trials, with transcranial direct current stimulation being effective in reducing pain and improving quality of life in patients with neuropathic pain, while transcranial magnetic stimulation has shown benefits in reducing pain in patients with neuropathic pain and chronic non-neuropathic pain (GALAFASSI G.Z. et al., 2021; MOISSET X. et al., 2019).

Transcranial stimulation uses magnetic pulses to modulate brain activity and has been investigated as a therapeutic approach for the treatment of neuropathic pain. This technique, which is based on the electromagnetic induction described by Faraday in 1831, involves the continuous application of an electrical stimulus for 20 to 30 minutes at a low intensity, through electrodes connected to the scalp. These electrodes produce electrical stimuli that reach various brain structures, both superficial (such as the prefrontal cortex, insula and cingulate cortex) and deeper (such as the thalamus and brainstem). The technique is easily transportable and can be administered by the patient in the home environment, enabling long-term treatment. Despite this, the level of evidence on the effectiveness of transcranial direct current stimulation is limited with regard to the treatment of chronic and refractory neuropathic pain, therefore, this is not a recommended technique for these cases (MOISSET X. et al., 2019).

Repetitive transcranial magnetic stimulation, in turn, is performed through a coil placed on the scalp, emitting a magnetic impulse capable of crossing the skull and reaching superficial cortical structures. This technique, lasting about 15 to 30 minutes, has been used to treat chronic neuropathic pain, such as complex regional pain syndrome and peripheral neuropathic pain. With evidence of effectiveness in reducing pain, the technique, however, still requires further studies to confirm its long-term effectiveness (MOISSET X. et al., 2019).

CONCLUSION

The field of neuropathic pain management is constantly evolving, aiming to reduce pain refractoriness and improve patients' quality of life. The better understanding of chronic pain and the advancement of current technologies allow us to offer more effective treatment options for patients. Management of chronic neuropathic pain involves both invasive and non-invasive approaches, with the aim of controlling symptoms. Initial measures are usually non-invasive, such as the use of antidepressants, anticonvulsants, and opioid analgesics. In cases of refractory pain, invasive interventions such as ablative procedures and neuromodulation are considered. Neuromodulation has been highlighted as a surgical option for refractory chronic pain, using pharmacological or electrical measures. Invasive techniques include motor cortex electrical stimulation, deep brain stimulation, and posterior insula stimulation, while non-invasive techniques involve transcranial stimulation and transcutaneous electrical nerve stimulation.

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