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Deep brain stimulation as a treatment for Parkinson's disease

Estimulação cerebral profunda como tratamento para a doença de Parkinson

Estimulación cerebral profunda como tratamiento para la enfermedad de Parkinson

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Abstract

Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disease and has been increasing in prevalence in recent decades. Deep brain stimulation (DBS) is an established treatment for severe Parkinson's disease (PD), dystonia, and tremor, and has an emerging role in a number of other neurological and neuropsychiatric conditions. However, its widespread adoption is currently limited by cost, side effects, and partial effectiveness. Objective: explain and describe the Deep Brain Stimulation method for the control and treatment of Parkinson's Disease. Search methodology: this is a descriptive research of the integrative literature review type, through online access to the PubMed, Scielo, CDSR, Google Scholar, VHL and EBSCO databases, in September 2021. Results and discussion: DBS can interact with pathological neural networks in a way that sometimes stimulates and sometimes inhibits certain pathways in order to eliminate or subdue the unwanted circuit in the basal ganglia loops, this mechanism became known as “blocking” the diseased network. Controlled stimulation reduces this hyperactivity and consequently removes noise, reestablishing the transmission of neural information and, consequently, returning movement control. Final considerations: the treatment consists of electrical stimulation in different regions of the

brain, for years without interruption. The electrical current used is very small, made at strategic points in the brain through the implantation of electrodes, which are, for the most part, deep.
Keywords: Neurosurgery; Deep brain stimulation; Parkinson's disease.

Resumo

Introdução: A doença de Parkinson (DP) é a segunda doença neurodegenerativa mais comum e tem vindo a aumentar em prevalência nas últimas décadas. A estimulação cerebral profunda (DBS) é um tratamento estabelecido para a doença de Parkinson (DP) grave, distonia e tremor, e tem um papel emergente em uma série de outras condições neurológicas e neuropsiquiátricas. No entanto, a sua adoção generalizada é atualmente limitada pelo custo, efeitos colaterais e eficácia parcial. Objetivo: explicar e descrever o método de Estimulação Cerebral Profunda para controle e tratamento da Doença de Parkinson. Metodologia de busca: trata-se de uma investigação descritiva do tipo revisão integrativa de literatura, por meio de acesso on-line às bases de dados PubMed, Scielo, CDSR, Google Acadêmico, BVS e EBSCO, em setembro de 2021. Resultados e discussão: DBS pode interagir com redes neurais patológicas em uma forma que às vezes estimula e às vezes inibe certas vias para eliminar ou subjugar o circuito indesejado nas alças dos gânglios da base, esse mecanismo ficou conhecido como "bloqueio" da rede doente. A estimulação controlada reduz essa hiperatividade e consequentemente remove ruídos, restabelecendo a transmissão das informações neurais e, consequentemente, devolvendo o controle do movimento. Considerações finais: o tratamento consiste na estimulação elétrica em diferentes regiões do cérebro, durante anos sem interrupção. A corrente elétrica utilizada é muito pequena, feita em pontos estratégicos do cérebro através da implantação de eletrodos, que são, em sua maioria, profundos.
Palavras-chave: Neurocirurgia; Estimulação cerebral profunda; Doença de Parkinson.

Resumen

Introducción: La enfermedad de Parkinson (EP) es la segunda enfermedad neurodegenerativa más común y su prevalencia ha ido aumentando en las últimas décadas. La estimulación cerebral profunda (ECP) es un tratamiento establecido para la enfermedad de Parkinson (EP), la distonía y los temblores graves, y tiene un papel emergente en otras afecciones neurológicas y neuropsiquiátricas. Sin embargo, su adopción generalizada está actualmente limitada por el costo, los efectos secundarios y la efectividad parcial. Objetivo: explicar y describir el método de Estimulación Cerebral Profunda para el control y tratamiento de la Enfermedad de Parkinson. Metodología de búsqueda: se trata de una investigación descriptiva del tipo revisión integrativa de la literatura, mediante acceso en línea a las bases de datos PubMed, Scielo, CDSR, Google Scholar, VHL y EBSCO, en septiembre de 2021. Resultados y discusión: DBS puede interactuar con redes neuronales patológicas en una forma que a veces estimula y a veces inhibe ciertas vías para eliminar o atenuar el circuito no deseado en los bucles de los ganglios basales, este mecanismo se conoció como "bloqueo" de la red enferma. La estimulación controlada reduce esta hiperactividad y en consecuencia elimina el ruido, restableciendo la transmisión de información neuronal y, en consecuencia, devolviendo el control del movimiento. Consideraciones finales: el tratamiento consiste en estimulación eléctrica en diferentes regiones del cerebro, durante años sin interrupción. La corriente eléctrica utilizada es muy pequeña, producida en puntos estratégicos del cerebro mediante la implantación de electrodos, que son, en su mayor parte, profundos.
Palabras clave: Neurocirugía; Estimulación cerebral profunda; Enfermedad de Parkinson.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease and has been increasing in prevalence in recent decades. It generally appears between 50 and 80 years of age, with a peak in the seventh decade of life. It is a disease with a higher incidence in males (1.4 to 1.0). Although there are studies that indicate the genetic factor is responsible for the onset of the disease in some cases, 90% of the time there is no identifiable genetic cause, which is why 90% of cases are attributed to other factors, such as environmental and epigenetics. Evidence indicates that head trauma, exposure to agricultural pesticides, and other toxins such as manganese lead to an increased risk of sporadic Parkinson's disease. In PD, there is a loss of dopaminergic neurons in the gray matter and there is an abnormal accumulation of aggregated alpha- synuclein in brain tissues, therefore belonging to the group of synucleinopathies (Aum et al., 2021).

Deep brain stimulation (DBS) is an established treatment for severe Parkinson's disease (PD), dystonia, and tremor, and has an emerging role in a number of other neurological and neuropsychiatric conditions. However, its widespread adoption is currently limited by cost, side effects, and partial effectiveness. In many brain disorders, for example PD, symptoms vary from moment to moment depending on factors such as cognitive and motor load and concomitant drug therapy. If it were feasible to track these fluctuations with an appropriate feedback signal and stimulate only when necessary, it would be possible

to improve therapeutic efficacy while preserving battery life and limiting side effects. A recent study in non-human primates suggested that adaptively controlled DBS, triggered by feedback from the spikes of a single motor cortical neuron, was even more effective than standard continuous high-frequency stimulation in a model of PD (Rammo et al., 2021).

In developing adaptive DBS (aDBS) for clinical use, two challenges must be overcome. First, the feedback signal must be robust over time. Second, neurosurgical intervention to the brain should be minimized to limit surgical risks, preferably using only a single surgical site. A possible solution to these problems is to record the local field potential (LFP) directly from the stimulating electrode and use it as a feedback signal to control when stimulation is delivered (Kogan et al., 2019). Therefore, this study aims to explain and describe the Deep Brain Stimulation method for the control and treatment of Parkinson's Disease.

2. Methodology

This is a descriptive research of the integrative literature review type, which sought to answer the objective of explaining and describing the Deep Brain Stimulation method for the control and treatment of Parkinson's Disease. The research was carried out through online access to the *National Library of Medicine* (PubMed MEDLINE), *Scientific Electronic Library Online* (Scielo), Cochrane Database of Systematic Reviews (CDSR), Google Scholar, Virtual Health Library (VHL) and EBSCO *Information Services,* in September 2021. To search for works, the keywords present in the descriptors in Health Sciences (DeCS) were used. in Portuguese: *"brain stimulation", "Parkinson's disease", "treatment", "neurosurgery"* and in English: *" brain stimulation ", " Parkinson's disease ", " treatment ", " neurosurgery ".*

As inclusion criteria, original articles were considered, which addressed the researched topic and allowed full access to the study content, published between 2012 and 2022, in English and Portuguese. The exclusion criteria were imposed on those works that were not in English or Portuguese, that had not gone through a Peer-View process and that were not related to the proposed theme. The article selection strategy followed the following steps: search in the selected databases; reading the titles of all articles found and excluding those that did not address the subject; critical reading of article summaries and full reading of articles selected in the previous stages. After careful reading of the publications, 5 articles were not used due to the exclusion criteria. Thus, there were a total of 20 scientific articles for the integrative literature review, with the descriptors presented above.

3. Results and Discussion

3.1 DBS mechanism of action

Initially, it is of interest to address the basis for the etiology of the signs and symptoms of Parkinson's Disease (PD), therefore, the molecular levels of dopamine are lower than expected in the nigrostriatal terminals of the basal ganglia. Thus, this deficiency causes abnormalities in the thalamocortical circuits of largely segregated basal ganglia, which causes an interruption of downstream network activity in the thalamus, cortex and brainstem. to get as close as possible to normality (Ramirez-Zamora et al., 2018). DBS stimulates some areas of the global corticobasal ganglia-thalamo-cortical network, with the subthalamic nucleus (STN) and the globus internal pallidus (GPi) are the most common forms of DBS (Malek et al., 2019; Rammo et al., 2021).

According to Wang et al. (2020), experimental work in the STN, showed that DBS can interact with pathological neural networks in a way that sometimes stimulates, sometimes inhibits certain pathways in order to eliminate or subdue the unwanted circuit in the basal ganglia loops, this mechanism became known as “blocking” the sick network. Stimulation would be aided by an implantable pulse generator (IPG), which would produce an electrical current, while inhibition would be caused

by a dissociation of input and output signals from the basal ganglia, resulting in interruption of the flow of abnormal information.

According to Aum et al. (2018), in some experiments to identify the primary targets of DBS, it was concluded that axons, rather than cell bodies, were probably more affected by electrical stimulation. Thus, multicompartmental cable modeling, which addresses signal transmission through discrete neuronal units, applied to thalamocortical relay neurons, revealed a reduction in activity in the somatosensory region, but an increase in axonal firing output, which was found to be synchronized with the stimuli.

3.2 Surgical technique

During surgery, the patient is normally awake, in parallel with this, a stereotaxic structure adjusted around the patient's head is used, which is followed by computed tomography and magnetic resonance images, which spatially integrate the structure based on a program software in order to provide brain coordinates and calculate possible probe trajectories, which assists in target accuracy (1 mm) (Pedrosa et al., 2013). Therefore, the ventral intermediate nucleus of the thalamus (VIM) is a target for essential tremor and parkinsonian tremor, but it is not effective in other motor characteristics, such as bradykinesia and rigidity, for this reason, the most common targets are the STN and the GPi, as they integrate more motor particularities (Malek et al., 2019).

According to Liu et al. (2020), neurophysiological verification is commonly achieved through intraoperative microelectrode recording (MER) followed by intracranial DBS electrode test stimulation (macrostimulation) to assess the benefits and side effects of electrical stimulation. With this, it is possible to guide the final positioning of the electrode, based on assessments of the clinical response, such as the improvement of symptoms such as stiffness, tremor and side effects due to DBS, which would involve waking the patient from anesthesia after approximately 1 or 2 hours. However, there is a divergence in the literature regarding this awakening, as some studies show that not using this technique could reduce operative time and also reduce the chances of intraoperative deep cerebral hemorrhage (Habets et al., 2018; İbrahimoğlu et al., 2020).

Regarding the benefits and harms of different surgical techniques, a relevant paradox would be the issue of wakefulness and sedation during surgery (Casner et al., 2018). Although general anesthesia has a lower probability of hemorrhage, local anesthesia is effective in terms of greater precision in electrode placement, fewer complications with the method of anesthesia itself, reduction in hospital stay, among others (Mehanna et al., 2013). Furthermore, according to a meta-analysis highlighted in the study by Houeto et al. (2012), there is an improvement in motor symptoms in patients undergoing STN DBS compared to GPi DBS, however, the difference was not statistically significant.

That is, the rationale for targeting specific structures within the basal ganglia, such as the subthalamic nucleus (STN) or the internal segment of the globus pallidus (GPi) is strongly supported by current knowledge of basal ganglia pathophysiology, which is derived from extensive experimental work that provides the theoretical basis for surgical therapy in PD (Kogan et al., 2019). In particular, STN has advanced to the most widely used global target for DBS in the treatment of PD, due to the marked improvement of all cardinal symptoms of the disease. Furthermore, menstrual period dyskinesias are reduced in parallel with a marked reduction in levodopa equivalent daily dose after STN-DBS (Okun et al., 2012). The success of the therapy largely depends on the selection of appropriate patient candidates and accurate implantation of the stimulation electrode, which requires careful imaging pre -targeting and extensive electrophysiological exploration of the target area (Schüpbach et al., 2015). Despite the clinical success of the therapy, the fundamental mechanisms of high-frequency stimulation are not yet fully elucidated (Silveri et al., 2012). There is a large amount of evidence from experimental and

clinical data that stimulation frequency represents a key factor with respect to the clinical effect of DBS (Abboud et al., 2014 ; Krack et al., 2013).

Interestingly, high-frequency stimulation mimics the functional effects of ablation on several brain structures. The main hypotheses for the mechanism of high-frequency stimulation are: (1) depolarization blockade of neuronal transmission through inactivation of voltage-gated ion channels, (2) information interference by the imposition of a high-frequency pattern triggered by efferent stimulation, (3) synaptic inhibition by stimulation of inhibitory afferents to the target nucleus, (4) synaptic failure by stimulation-induced neurotransmitter depletion. As STN hyperactivity is considered a functional hallmark of PD and there is experimental evidence of excitotoxicity STN-mediated glutamatergic drive in neurons of the substantia nigra pars Compacta (SNc), STN-DBS can reduce glutamatergic drive, leading to neuroprotection. Further studies will be needed to elucidate whether STN-DBS truly provides a slowing of disease progression (Odekerken et al., 2013; Asahi et al., 2014).

4. Final Considerations

DBS is applied using very delicate electrodes and therefore does not damage or harm brain tissue. Instead, it blocks the faulty signals that cause tremors and other symptoms. In Parkinson's disease, due to the lack of dopamine, there is difficulty in communication between the brain structures that, as a network, control movement. This change causes hyperactivity of certain brain nuclei compared to noise or interference as occurs in radio transmission and telecommunications. Controlled stimulation reduces this hyperactivity and consequently removes noise, reestablishing the transmission of neural information and, consequently, returning movement control. Thus, the treatment consists of electrical stimulation in different regions of the brain, for years without interruption. Furthermore, the electrical current used is very small, made in strategic points of the brain through the implantation of electrodes, which are, for the most part, deep.

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