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ORIGINAL ARTICLE

Deep brain stimulation for Parkinson's disease: experience, benefits and limitations in a center in Latin America

Estimulación cerebral profunda para enfermedad de Parkinson: experiencia, beneficios y limitaciones en un centro en Latinoamérica

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Abstract

Background: *Parkinson's disease is poorly studied in Colombia. It is pharmacologically managed, but for refractory cases, surgery is a therapeutic option, positively impacting on quality of life.* **Objective:** *To determine the impact of deep brain stimulation as management in the control of progression in patients with Parkinson's disease attended our institution between the years 2014 to 2020.* **Method:** *Descriptive retrospective study, with patients collected between 2014 and 2020 undergoing deep brain stimulation surgery. The MDS-UPDRS (Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale) was applied in the preand postoperative period, and the results were compared.* **Results:** *21 patients were included and the UPDRS was applied, finding a decrease in scores in the postoperative period. One patient had an operative site infection.* **Conclusions:** *There was an improvement in the MDS-UPDRS score, with a low rate of complications. The procedure time was prolonged from the preoperative evaluation. Deep brain stimulation is the management of choice for refractory Parkinson's disease. The patients in this series showed improvement in their symptoms. Unfortunately, there are limitations to perform this procedure in Colombia, such as the delay in the authorization of the procedure.*

Keywords: *Parkinson Disease. Deep brain stimulation. Tremor.*

Resumen

Antecedentes: *La enfermedad de Parkinson está poco estudiada en Colombia. Es de manejo farmacológico, pero para casos refractarios la cirugía es una opción terapéutica que impacta positivamente en la calidad de vida.* **Objetivo:** *Determinar el impacto de la estimulación cerebral profunda como manejo en el control de la progresión en pacientes con enfermedad de Parkinson atendidos nuestra institución entre los años 2014 a 2020.* **Método:** *Estudio descriptivo de corte retrospectivo con pacientes recolectados entre los años 2014 y 2020 sometidos a cirugía de estimulación cerebral profunda. Se aplicó la MDS-UPDRS (Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale) en el prey el posoperatorio, y se compararon los resultados.* **Resultados:** *Se incluyeron 21 pacientes y se les aplicó la MDS-UPDRS, encontrando una disminución en las puntuaciones en el posoperatorio. Un paciente presentó infección del sitio operatorio.* **Conclusiones:** *Hubo mejoría en la puntuación de la MDS-UPDRS, con baja tasa de complicaciones. El tiempo de realización del procedimiento fue prolongado desde la valoración preoperatoria. La estimulación cerebral profunda es el manejo de elec-*

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ción para la enfermedad de Parkinson refractaria. Los pacientes de esta serie mostraron mejoría en sus síntomas. Desafortunadamente, existen limitaciones para la realización de este procedimiento en Colombia, como el retraso en la autorización del procedimiento.

Palabras clave: *Enfermedad de Parkinson. Estimulación cerebral profunda. Temblor.*

Introduction

Parkinson's disease (PD) was first described in 1817 by James Parkinson[1]. It is the second most common neurodegenerative disease worldwide, with a prevalence of 150 cases per 100,000 inhabitants[2,3]. In European countries, prevalence ranges from 65.6 up to 12,500 cases per 100,000 inhabitants[3]. In Colombia, the EPINEURO trial conducted in 2003 reported a prevalence of 4.4 cases per 100,000 inhabitants[4], and another study conducted in the Antioquia region in 2004 reported 30.7 cases per 100,000 inhabitants[5]. Physiologically, PD involves dysfunction of the basal ganglia due to dopamine depletion[6]. In this circuit, the main nuclei involved are the striatum (caudate and putamen), the subthalamic nucleus (STN), the external globus pallidus (GPe), the internal globus pallidus (GPi), and the substantia nigra[7] (Fig. 1). The pathways are further segregated into 5 major pathways: 1) the motor pathway, which has a dorsolateral position with projections to the primary motor cortex and supplementary motor area; 2) the oculomotor loop, centered on the caudate nucleus, connecting with the frontal eye fields; 3) the dorsolateral prefrontal loop, also connecting the caudate with the dorsolateral prefrontal and posterior parietal cortices; 4) the orbitofrontal loop, mainly connecting the caudate with the orbitofrontal cortex; and 5) the limbic loop, connecting the anterior cingulate, temporal lobe, and orbitofrontal cortex with the basal ganglia[8].

Additionally, inside the basal ganglia, 3 major pathways are classically known: the direct pathway, which mainly stimulates movement, and the indirect and hyperdirect pathways, which inhibit movement contrary to the direct pathway[8]. In PD, the lack of dopamine results in the hyperactivity of the STN and the GPi/substantia nigra reticular complex, leading to thalamocortical inhibition and an imbalance between the direct, hyperdirect, and indirect pathways[9,10], clinically manifesting as bradykinesia, muscle rigidity, resting tremor, and postural instability, among other clinical signs.

Although pharmacological treatment for PD remains the standard today, too many cases show refractoriness within the first and second decades of the disease, prompting the development of new therapeutic techniques such as deep brain stimulation (DBS), a procedure that involves stimulating 1 of 3 therapeutic targets: the ventral intermediate nucleus, the GPi, or the STN[7,11]. DBS has shown to improve both motor control and spasticity[12], enhancing the patients and their families' quality of life.

In Colombia, like in many low- and middle-income countries, there are multiple limitations, primarily associated with the high cost of performing this surgery. In Colombia, the health care system is built on 2 regimes: private contributory and public subsidized. Additionally, there are different health service providers (EPS) responsible for managing various health service institutions to provide all health services. To perform DBS in Colombia, authorization from the EPS is required, which can often delay the procedure.

Therefore, the objective of this study was to determine the impact of DBS on symptom progression control in a series of PD patients treated at our institution and to describe the limitations in performing this procedure in a Colombian institution.

Method

We conducted a retrospective descriptive study. Inclusion criteria were patients older than 18 years with PD, refractory to medical treatment, without associated dementia syndrome, who had not previously undergone DBS surgery, and who underwent unilateral or bilateral DBS in our center from 2014 through 2020. All procedures were performed by a functional neurosurgeon (OZ) and involved macro- and microrecording stimulation (Fig. 2).

The procedure was performed in 2 surgical acts. First, stimulation with recording, using a Leksell frame guided by preoperative computed tomography and magnetic resonance imaging, both with fine-cut protocols for Parkinson's surgery; the recording is conducted and the therapeutic target is reached. Subsequently, the generator is placed, which according to the surgeon's experience can be rechargeable or non-rechargeable.

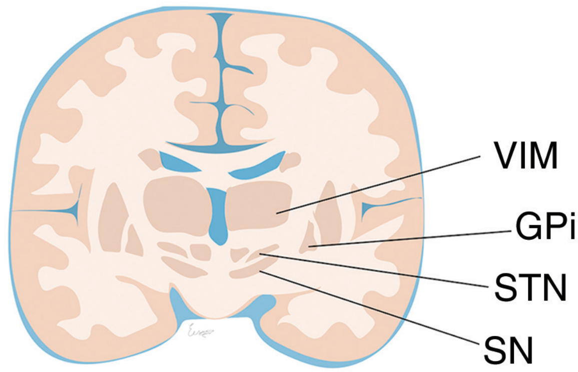

Figure 1. *Targets for deep brain stimulation in Parkinson's disease. GPi: internal globus pallidus; STN: subthalamic nucleus; VIM: ventral intermediate nucleus; SN: substantia nigra.*

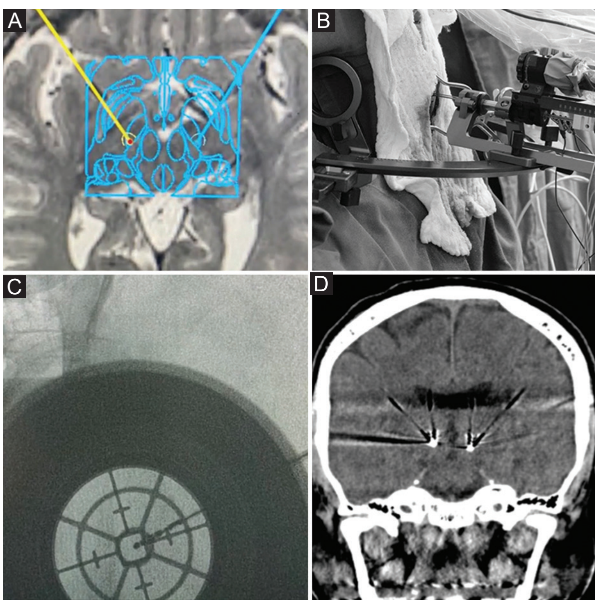

Figure 2. *Pre-, intra-, and postoperative images of deep brain stimulation for Parkinson's disease.* **A:** *planning for the bilateral localization of the subthalamic nucleus.* **B:** *intraoperative photograph with the Leksell stereotactic frame for macroand microrecording.* **C:** *intraoperative radiological confirmation of the stereotactic localization of the electrode tips.* **D:** *postoperative tomography to evaluate the correct trajectory and location of the electrodes.*

Patients who had undergone previous DBS in a different center and those with other movement disorders were excluded. Demographic data such as sex, age, laterality, clinical presentation characteristics, and any surgical or non-surgical complications were collected via electronic heath record review. For objective symptom follow-up, the MDS-UPDRS (Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale) and the Hoehn and Yahr scale were used, recording each item at 3 different time frames: preoperatively, 30 days after surgery, and 60 days after surgery.

All information was entered into an Excel database, with space and coding for each variable for subsequent statistical analysis in Stata 17.0. The analysis consisted of 2 parts: 1) initially, quantitative variables were expressed as mean and confidence intervals, and qualitative variables were expressed as frequency and percentage with their respective confidence intervals, and 2) the means of the MDS-UPDRS scores preoperatively, 30 days, and 60 days after surgery were obtained and compared to see if there was a decrease in these scores (using paired t-test).

Results

Twenty-one patients with a mean age of 53.71 ± 9.93 years were included, most being male (61.9%). All patients belonged to the contributory regime within the health care system, coming from private EPS. A total of 100% of patients had a preoperative clinical course of the disease with a mean of 10 ± 3.47 years (range, 6-20). Of the 21 patients, surgery was performed using a rechargeable generator in 47.6% and a non-rechargeable generator in 52.4%, based on the surgeon's preference. Of note that in DBS surgery, a pulse generator is used to send energy to the therapeutic target, which can be rechargeable, with a longer duration (approximately 9 years) vs the non-rechargeable, which typically lasts between 3 and 5 years before replacement. Additionally, preoperative and postoperative drug use was evaluated, showing no decrease in levodopa and carbidopa use, but a trend towards a lower use of other evaluated drugs (amantadine, biperiden, entacapone, pramipexole, rotigotine, and rasagiline) without statistical significance ($p > 0.05$). There was also a trend towards a reduction in the number of drugs used by patients when comparing pre- and postoperative states, without statistical significance ($p > 0.05$).

The clinical aspects of the patient were also evaluated: tremor, rigidity, and bradykinesia. All these 3 symptoms were present in 100% of patients in the preoperative state. Improvement was observed in patients, with a reduction of 71.4% for tremor, 57.1% for rigidity, and 71.4% for bradykinesia ($p = 0.0010$) (Table 1). An analysis was also performed on the data obtained from applying the MDS-UPDRS to patients at the 3 different evaluated points (preoperative, 30 and 60 days after surgery), while the paired t-test and

Wilcoxon test were used to compare: 1) the preoperative state with the state at 30 days postoperative, 2) the preoperative state with the state at 60 days after surgery, and 3) the 2 postoperative states. Comparing the preoperative state with the state 30 days after surgery showed a difference with a decrease in the patients' mean MDS-UPDRS scores: 58.8 ± 21.2 vs 45.9 ± 11.2. Compared with the state 60 days after surgery, it also showed a decrease in the scale from 58.8 ± 21.2 down to 34.0 ± 12.7. Finally, comparing the 2 postoperative states showed a decrease between them from 45 ± 11.2 down to 34.04 ± 12.7. Within the MDS-UPDRS, the findings that generated the most changes in these scores were aspects related to both symptomatology and physical exploration of the motor aspect, mainly in the parts of tremor, rigidity, and bradykinesia, corresponding to the 3 main symptoms of the disease. All these results had a p-value < 0.005 (Table 2).

Finally, we should mention that only 1 out of the 21 patients evaluated in the study presented a complication (4.8%) during the entire follow-up period until 60 days: an infection at the surgical site. Also, all 21 patients evaluated underwent bilateral DBS in the STN, thus achieving stimulation of the therapeutic targets.

Table 1. Comparison of outcomes for tremor, rigidity, and bradykinesia in patients between preoperative and postoperative states

Clinical Aspect	Preoperative	Postoperative	p
Tremor			0.0001
Proximal	-	1 (5%)	
Distal	21 (100%)	5 (24%)	
No tremor	-	15 (71%)	
Rigidity			0.0001
Yes	21 (100%)	9 (43%)	
No	-	12 (57%)	
Bradykinesia			0.0001
Yes	21 (100%)	6 (29%)	
No	-	15 (71%)	

Table 2. Mean scores of MDS-UPDRS scale applied preoperatively and 30 and 60 days after surgery

Comparison	Patients	Mean	SD	95%CI
Preoperative vs. 30 days				
Preoperative	21	58.8	21.2	49.15 68.46
30 days	21	45.0	11.2	40.83 51.06
Difference	21	13.8	12.5	7.16 18.54
Preoperative vs. 60 days				
Preoperative	21	58.8	21.2	49.15 68.46
60 days	21	34.0	12.7	28.22 39.86
Difference	21	24.7	22.3	14.61 34.91
30 vs. 60 days				
30 days	21	45.9	11.2	40.83 51.06
60 days	21	34.0	12.7	28.22 39.86
Difference	21	11.9	1.5	6.11 17.69

SD: standard deviation; 95%CI: 95% confidence interval.

Discussion

In this study, we found that the mean age of presentation was older than 50 years (53.7 years), with a slight male predominance. In the EPINEURO trial, PD was documented in people older than 60 years, mainly from northwest Colombia, with a male predilection[4]. However, observing the number of patients documented in both studies, it should be clarified that no conclusions can yet be drawn about the condition of the Colombian population, which is biased by its geographic location and the state of the disease. Worldwide, this condition is known to affect approximately 1 or 2 people per 1000 inhabitants and affects 1% up to 3% of the population older than 60 years[13]. This study included surgical patients referred to our institution based on their EPS contract. This study also evaluated the time elapsed between the first consultation by the functional neurosurgery group that indicated the procedure and the moment it was performed to find that the average waiting time for patients in the center was 6.2 months. Additionally, we should mention that some patients not included in the study did not get authorization or had to be referred to a different center.

On the other hand, our study patients showed clinical improvement (71.4% for tremor, 57.1% for rigidity, and 71.4% for bradykinesia; p = 0.001) and a reduction in medication use after surgery, implying a higher quality of life for the patient, which was also reflected in better adherence to pharmacological treatment and a reduction in adverse effects from this therapy, such as nausea, hypotension, headache, and lower limb edema, among others.

Regarding the evaluation with the MDS-UPDRS, a meta-analysis of 16 studies showed statistically significant efficacy, with a reduction of 4 points in the scale after DBS in the GPi or STN[14]. In our study, no change was observed for the emotional component (depression and anxiety), as none of the patients presented such symptoms pre- or postoperatively. However, worldwide literature indicates that DBS, particularly when stimulating the GPi, is associated with improvement in mood and behavior disorders[15]. Regarding the patient's clinical condition evaluated with the MDS-UPDRS, we found statistically significant improvement in both symptoms and quality of life. Similarly, the meta-analysis published by Bratsos et al.[16] found an overall improvement in MDS-UPDRS scores in patients who underwent DBS compared to those on optimal medical therapy. However, we should mention that although this type of management offers symptomatic improvement, it does not influence the natural course or progression of the disease; hence, it does not have a curative intent[17].

Moreover, it has been observed that, generally, surgery is a safe procedure. The most common complication is overstimulation of the surrounding brain tissue (50%), followed by cerebral hemorrhage and infection, which are very infrequent[13]. In our study, no vascular complications or overstimulation were evident; there was only 1 case of surgical site infection, which is expected in our series and comparable to what is reported in other studies.

Finally, it is important to remember that DBS surgery is a palliative treatment, meaning it serves to improve the patient's quality of life and symptoms but does not modify the progression of the disease. Ultimately, this condition will continue its inevitable progression, and it is necessary to clarify that this study follows up for 60 days, during which improvement was observed, but a long-term study would show disease progression manifested by patient deterioration.

DBS in Colombia and Latin America

Various functional neurosurgery teams are in the region, highlighting groups from Mexico[18,19], Argentina[20], and Chile[21,22], among others. The development of multidisciplinary groups, including neurologists, psychiatrists, and neurosurgeons, has made the subspecialty move forward. Despite the low incidence and prevalence of the disease and the small number of patients requiring surgical management, other movement disorders and the development of epilepsy and pain surgical interventions have increased procedures such as DBS and epilepsy surgery in Latin America.

Currently, DBS surgery is performed in various parts of the country, such as Barranquilla[23], Bucaramanga[24], Medellín, Pereira, Cali, and Bogotá[25]. Despite the widespread performance of the procedure in all major cities, access through the healthcare system is limited due to the high cost of the procedure. Each surgery can cost around USD 30,000, which comparatively represents more than 100 times the minimum wage in Colombia. Despite these costs, a systematic review showed that various studies have demonstrated that DBS surgery is cost-effective vs the best medical therapy[26]. Therefore, DBS surgery should continue to be considered the best alternative despite all the limitations in low- and middle-income countries like Colombia.

Limitations for performing DBS in middle-income countries

First, one of the main limitations for performing this procedure in middle-income countries is the lack of multidisciplinary teams to address and manage patients with this condition. Given the high specialization level of this procedure, few centers have the necessary personnel and resources to perform the surgery and provide adequate follow-up. Second, it is important to highlight that DBS is a high-cost procedure, with the stimulator alone costing up to USD 20,000, leading to difficulties in obtaining authorization for the procedure. Finally, this procedure typically requires periodic follow-ups for proper patient management, and often the problem arises that the follow-ups are conducted in institutions different from where the surgery was performed, or patients return to their place of origin, which can be in rural areas. This results in difficulty in comprehensive postoperative management and loss of patient adherence to follow-up, hindering the clinical and epidemiological continuity of the patients.

Study limitations

The first limitation of this study is that the information collected was obtained retrospectively, and it is possible that some data were not fully available to conduct a proper analysis of all variables. The second is that, due to multiple factors, many patients are lost to follow-up, making it impossible to perform longer-term controls, which would allow for more extensive and rigorous future analysis. Additional studies are needed in our country that are not only descriptive but also have a long-term follow-up component with a larger number of patients to establish standardized figures adapted to our national and regional context. Despite these limitations, we consider this study represents the characterization and evaluation of many obstacles in Latin American countries to performing DBS in PD patients.

Conclusions

Our center experience demonstrates that DBS is a viable and effective option for improving symptoms and quality of life in PD patients. Despite delays in the procedure due to EPS authorizations, patients showed statistically significant clinical improvement and a trend towards reducing the number of drugs after the intervention. Future regional multicenter studies are needed to highlight all the limitations for performing DBS in Latin American countries.

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Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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