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Research Article

Effect of bilateral deep brain stimulation on the subthalamic nucleus on patients with Parkinson's disease: An observational and non-blinded study

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ABSTRACT

Objective: This study analyzed the influence of subthalamic nucleus deep brain stimulation (DBS) in motor parameters and patients' quality of life with Parkinson's disease (PD) evaluated before and after 12 months of the surgical procedure.

Methods: A cohort of 20 patients with PD who underwent DBS implantation in the subthalamic nucleus was included. Pre and *on*-DBS postoperative data in *on* and *off*-medication periods related to motor functions and quality of life, from the application of validated scales, were collected to verify possible relationships between changes in these parameters and the surgical procedure.

Results: A significant decrease in the Hoehn and Yahr scale disease stage and in the levodopa equivalent dose ($p < 0.001$) was verified in the *off*-medication period when we compared baseline and post-12 months data. A significant decrease in dyskinesias ($p = 0.009$) was observed during the *on*-medication period by evaluating the UDysRS scale. Concerning motor functions verified through the UPDRS-III scale, it was obtained a significant reduction in total scores ($p = 0.001$), besides a decrease in rigidity scores for upper and lower limbs ($p < 0.05$) during the *on*-medication period. During the *off*-medication period, scores of UPDRS-III demonstrated a significant decrease, except for the ones related to speech and amplitude of resting tremor. Regarding the quality-of-life assessment, scores obtained from PDQ-39 showed that, after 12 months of electrode implantation, there was a significant decrease in mobility, daily living activity, and stigma parameters ($p < 0.05$).

Conclusions: Results obtained allow us to conclude that DBS of the subthalamic nucleus in patients with PD improves motor function in both *on* and *off*-medication periods, improvement of the disease stage in the *off*-medication period, with no change in the *on*-medication period, also an improvement in the patient's self-reported quality of life and a significant reduction in the dose of L-DOPA.

1. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease globally, behind only Alzheimer's disease [1]. PD currently affects more than 6 million people globally [2], and it is estimated that more than 12 million individuals are diagnosed by 2050 [3]. Because it is a neurodegenerative disease and since the world population is aging, an exponential increase in PD prevalence is projected in the coming decades [4].

PD is a progressive and disabling condition, which significantly impairs motor and non-motor functions, impacting the patient's quality of life [5,6]. Motor symptoms include involuntary tremor, bradykinesia, postural instability, and intense difficulty in initiating movements [7–9], while non-motor signs include sleep-wake cycle instability, cognitive impairments, such as cognitive deficits, memory, dementia, and hallucinations, anxiety, orthostatic hypotension, mood disorders, autonomic dysfunctions, and sensory symptoms, such as pain and partial loss of smell [10–12].

Levodopa (L-DOPA) is the primary therapeutic approach for treating PD motor symptoms since it has a beneficial effect on many symptoms,

Abbreviations: DBS, deep brain stimulation; L-DOPA, levodopa; LED, levodopa equivalent dose; LLL, left lower limb; LUL, left upper limb; PD, Parkinsońs disease; PDQ-39, Parkinson's Disease Questionnaire-39; RLL, right lower limb; RUL, right upper limb; UDysRS, Unified Dyskinesia Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

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especially stiffness and akinesia [10]. However, it has been observed that after some time of using L-DOPA, its effect decreases, and patients experience some side effects, such as motor fluctuations, including dyskinesia and wearing-off phenomena, and non-motor fluctuations, such as dysautonomia, cognitive and psychiatric, and sensory/painful [13–15].

Therefore, other options have been increasing in the last decades as methods to relieve symptoms and improve patients' quality of life, including the practice of physical activities [16], the approach by multidisciplinary teams [17], the treatment of non-motor symptoms, and other comorbidities [18], and surgical procedures, such as deep brain stimulation (DBS). DBS modulates disordered activities of the basal ganglia [19,20], mainly in the region of the subthalamic nucleus and the Globus Pallidus internus (GPi) [21]. The subthalamic nucleus has a regulatory role, providing inhibitory signaling in the cortico-subcortical networks of the basal ganglia [22].

Ideal candidates for DBS in the subthalamic nucleus are patients with an established diagnosis of PD for at least four years with no dementia, cognitive deficits, or severe depression, presenting motor complications, unsatisfactory control, and/or intolerance to drug treatment [23]. In order to minimize the risk of cognitive changes or aggravating depression in the postoperative period in patients with a significant history of depression or mild dementia and also among patients of advanced age, DBS in the GPi is more indicated than DBS in the subthalamic nucleus [24].

DBS has shown benefit in mitigating motor symptoms [19,25,26], significantly improving mobility [20,27,28] and reducing dyskinesias [20,27] for long post-procedure periods [25,29], and increasing the quality of life to the patient [14]. Previously studies have shown a risk–benefit relationship favorable to the performance of the surgical procedure, especially concerning the patient's quality of life [30], including when the procedure is compared to the best available therapy [20,27] or associated to it [31].

The present study aimed to analyze the influence of bilateral deep brain stimulation on the subthalamic nucleus in motor functions and the quality of life of patients with Parkinson's disease in Brazil evaluated before and after 12 months after the surgical procedure, data that are scarce in Brazilian and world literature.

2. Materials and methods

2.1. Study population

An observational prospective cohort study with patients with PD was performed at the Movement Disorder sector of Hospital São Paulo, Brazil. After a multidisciplinary evaluation with a specialized neurologist in movement disorder, functional neurosurgeon, neuropsychologist, and nursing team, 24 patients with an established diagnosis of PD for at least four years and four months, exhibiting on and off-medication motor fluctuations, such as wearing off and/or dyskinesias (despite the use of optimized anti-Parkinsonian medication) and/or refractory tremor to medication use, or significant side effects with optimized medications, well-motivated with the surgery, with caregivers, between 18 and 75 years old that understand the study and verbalize the consent, were included in the study. Patients who refused to answer the questionnaire with dementia or severe psychiatric disorders, were excluded from the study. Incomplete patient data were excluded from the final analysis. All patients consented to participate in this study through the ICF. Institutional review board approval from UNIFESP (n° 3.343.148) was obtained before the study started.

2.2. Surgical technique

The neurosurgical procedure was performed as previously described [32,33]. In summary, the intended target coordinates were determined based on 3 T magnetic resonance imaging (MRI) (Phillips, Achieva, USA). After finding the commissural midpoint, through the landmarks of the anterior and posterior commissures, the targets were calculated indirectly and corrected according to the anatomy of each patient [34]. The electrodes (models 3389 Medtronic, Minneapolis, MN, USA) were implanted using the Leksell stereotaxic arch (Elekta, Sweden) in the subthalamic nucleus under local anesthesia of 0.5% bupivacaine associated with sedation with dexmedetomidine. All patients underwent intraoperative neurophysiological study using the microrecording technique using one to three microelectrodes (LeadPoint, Medtronic, Minneapolis, MN, USA) to establish neurophysiological confirmation of the dorsal and ventral region of the nucleus, in addition to confirmation of the sensory-motor region through passive stimulation of the limbs. After the neurophysiological examination mentioned above, intraoperative stimulation tests were performed, still with the microelectrode, with pre-established parameters of monopolar configuration, with frequency 130 Hz, a pulse width of 60 μs, ensuring an excellent therapeutic window. The therapeutic window was clinically confirmed after clinical improvement of PD symptoms such as rigidity, tremor and/or bradykinesia, and the onset of side effects of corticobulbar and/or corticospinal pathway involvement, such as speech, gaze deviation, rhyme deviation, worsening of motor tone, and/or contralateral limb contraction, paresthesia or neurovegetative symptoms.

After choosing the best trajectory, deep brain electrodes were inserted. Intraoperative macro-stimulation was used to reconfirm the target's position, with bipolar parameters, frequency of 130 Hz and pulse width of 90 μs, with the most ventral contacts being tested and, later, the contacts that obtained the best therapeutic window in the previous test. The programmable pulse generator (Medtronic, Minneapolis, MN, USA) was implanted in the subclavicular region under general anesthesia in a second moment, with an interval of three to four weeks after the initial procedure. The programming started with the monopolar form contact test, where the pre-set parameters were a pulse width of 60 μs, frequency of 130 Hz, and progressive increase in voltage with 0.5 V increments, to establish the parameters of the therapeutic window situated between the beginning of improvement in PD symptoms and the beginning of the presence of side effects.

Finally, the best electrode contact was chosen, and the one with the best therapeutic response with the minimum stimulation load was selected. Special attention was given to the observation of dyskinesia, which was considered to announce the effectiveness of this contact. The electrical parameters (amplitude, pulse width, and frequency) were subsequently adjusted using the DBS programmer (Medtronic, Minneapolis, MN, USA). DBS programming parameters and electrode impedance were systematically documented, covering a 12-month follow-up period. The programming visits followed 30 days, 3, 6, 9, and 12 months after surgery. The image to confirm the satisfactory placement of the electrodes on the target was made through the acquisition of a non-contrast-enhanced postoperative cranial computed tomography (Philips Brilliance, 40 and 64 channels, USA) whose image was merged with preoperative brain MRI through Suretune software (Medtronic, Minneapolis, MN, USA).

2.3. Data collection instruments

For analysis of the influence of bilateral DBS in the subthalamic nucleus in relation to motor functions and quality of life, patients with PD were evaluated before the surgical procedure (between 30 and 60 days before the procedure) and 12 months later.

Patients were evaluated in a non-blind manner before surgery in *off*-medication and *on*-medication conditions and after the surgery in *off*-medication/*on*-DBS, *off*-medication/*off*-DBS, *on*-medication/*on*-DBS and *on*-medication/*off*-DBS conditions, always following the same order.

The analysis was performed using the following scales as previously described: Unified Parkinson's Disease Rating Scale (UPDRS) part III [35,36], Unified Dyskinesia Rating Scale (UDysRS) [36,37], Modified

Hoehn and Yahr Scale [13], The Parkinson's Disease Questionnaire (PDQ-39) [38,39], and daily Levodopa Equivalent Dose (LED) [40]. During the application of UPDRS III, UDysRS, and modified Hoehn and Yahr scale the clinical status of the patient was set to *on* or *off*-medication.

2.4. Statistical analysis

The clinical characterization of the sample was performed by descriptive analyzes. To compare each participant's data, in pre and postoperative periods, whenever possible, analysis were performed using the student's *t*-test for paired samples or Wilcoxon test in absence of the assumption of normality of the data. Correlation among PDQ-39 and baseline factors was evaluated using Spearman's correlation. The Minitab statistical software, version 18.1, was used for data analysis, and statistical significance was considered for p values ≤ 0.05.

3. Results

3.1. Study population

From November 2014 to March 2018, 48 patients with PD underwent surgery in the Movement Disorder sector of Hospital São Paulo, 24 (50%) of which underwent DBS implantation in the bilateral subthalamic nucleus for PD. Four patients were excluded from the analyses, two due to infection of the neurostimulation system requiring device explantation, and two due to lack of follow-up. Twenty patients (41.5%) who underwent DBS and completed the follow-up were included in the final analyses. Demographic and clinical data collected before DBS were presented in Table 1.

Table 1
Baseline information of patients included in the final analysis.

Total of patients (N, %)	20 (100%)
Sex (N, %)	
Male	16 (80%)
Female	4 (20%)
Age at the beginning of PD (Years)	
Mean ± SD	42.2 ± 11.4
Min.-Max.	24–68
Median	42
Disease duration (Years)	
Mean ± SD	10.5 ± 5.0
Min.-Max.	4–25
Median	10
Levodopa equivalent dose (mg)	
Mean ± SD	1105 ± 393
Min.-Max.	100–1725
Median	1175
UPDRS III (Mean ± SD)	
on-medication period	26.1 ± 11.7
off-medication period	57.4 ± 16.3
Hoehn and Yahr scale (Mean ± SD)	
on-medication period	2.3 ± 0.5
off-medication period	3.1 ± 0.6
UDysRS (Mean ± SD)	
on-medication period	9.55 ± 11.2
PDQ-39 (mean ± SD)	
Mobility	52.2 ± 23.5
Daily living activity	47.9 ± 27.8
Emotional	38.0 ± 17.8
Stigma	41.0 ± 30.3
Social	22.9 ± 22.9
Cognition	18.5 ± 16.4
Communication	29.1 ± 25.4
Pain	46.3 ± 23.2
Total score	42.32 ± 14.25

3.2. Motor and quality of life evaluation

Before the surgical procedure and 12 months after the DBS implantation, all patients included in this study underwent evaluations of motor functions in *on* and *off*-medication periods, quality of life, and evaluation of daily levodopa equivalent dose (LED). The following evaluations in *on* and *off*-medication periods 12 months after the surgical procedure were performed on *on*-DBS condition.

The UPDRS III scale is considered the standard gold scale for assessing and monitoring disability and impairment related to PD, whether in early or advanced stages. The total score of the UPDRS III in the baseline and 12 months after the surgical procedure in *on*-DBS period showed a statistically significant decrease in both *on* and *off*-medication periods ($p \leq 0.001$) (Fig. 1).

Significant decreases in the scores between pre and postoperative periods were observed in the on-medication period only for the following functions: stiffness of the right upper limb (RUL), left upper limb (LUL), right lower limb (RLL) and left lower limb (LLL) and resting tremor amplitude in the LUL. In the off-medication period, except for speech parameters and amplitude of tremor at rest on the lip, all parameters evaluated showed a significant decrease in the scores compared to pre and postoperative periods. Both exceptions showed an average reduction in the score but without significant difference statistics. The results of all parameters can be seen in Table 2.

The assessment of dyskinesias measured using the UDysRS scale showed a significant decrease of 78% ($p = 0.009$) in the *on*-medication period 12 months after the surgical procedure (Fig. 2). In the off-medication period, only two participants had pre and postoperative scores. One reduced the score from 5 to 0 after 12 months, and the other obtained score of 2 in pre and postoperative periods.

The assessment of patient disability in the off-medication period, measured using the modified Hoehn and Yahr scale, showed a statistically significant difference when comparing the pre and postoperative periods, reducing from median 3 for 2 ($p < 0.001$). In the *on*-medication period, the evaluation showed no statistically significant difference (Table 3).

Patients' quality of life was assessed using the PDQ-39 questionnaire. It is the most used questionnaire to evaluate the quality of life of a patient with PD. There was a significant reduction ($p = 0.001$) in the average total score from the preoperative to the postoperative period (Fig. 3a). This reduction indicates an improvement of approximately 50% in the patient's self-reported quality of life after 12 months. Analyzing each domain of the questionnaire, a significant reduction in scores was observed in the following domains: mobility ($p < 0.001$), the activity of daily living ($p < 0.01$), and stigma ($p < 0.01$). The other

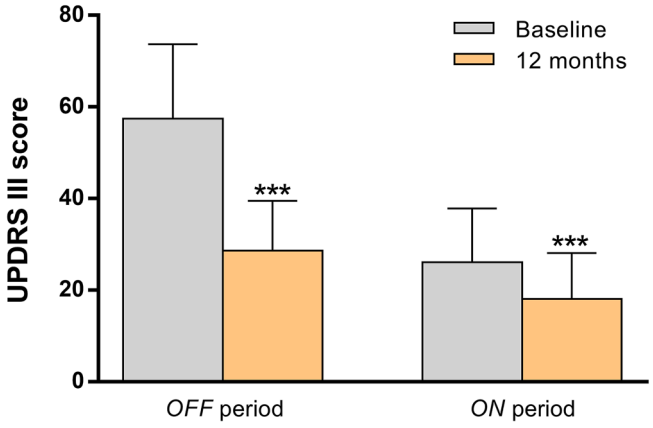

Fig. 1. Motor assessment score using UPDRS III in *on* and *off*-medication periods. The data correspond to the mean ± standard deviation (SD) obtained preoperatively (baseline) and *on*-DBS postoperatively (12 months). *** $p < 0.001$, paired Wilcoxon test.

Table 2
Scores on UPDRS-III scale (motor functions) in on-medication and off-medication periods.

Period	*ON*-medication			*OFF*-medication		
Parameters (mean ± SD)	Baseline	12 months	p-value[1]	Baseline	12 months	p-value[1]
Speak	0,9 ± 0,6	1,0 ± 0,6	0,281	1,6 ± 0,6	1,4 ± 0,7	0,285
Face	1,2 ± 0,6	1,0 ± 0,5	0,450	2,3 ± 0,6	1,8 ± 0,6	0,031
Neck	1,1 ± 0,7	1,0 ± 0,8	0,865	2,2 ± 0,8	1,3 ± 0,8	0,004
RUL stiffness	0,8 ± 0,6	0,3 ± 0,6	0,031	1,9 ± 0,7	0,7 ± 0,7	<0,001
LUL stiffness	1,0 ± 0,7	0,6 ± 0,6	0,042	2,2 ± 1,0	0,9 ± 0,7	0,001
RLL stiffness	0,9 ± 0,6	0,3 ± 0,4	0,01	2,0 ± 0,8	0,8 ± 0,6	<0,001
LLL stiffness	1,2 ± 0,8	0,6 ± 0,5	0,004	2,3 ± 0,9	1,0 ± 0,8	0,001
Right hand tapping fingers	1,1 ± 0,7	1,0 ± 0,9	0,756	2,3 ± 0,8	1,4 ± 0,9	0,003
Left hand tapping fingers	1,5 ± 1,1	1,1 ± 1,0	0,182	2,4 ± 1,0	1,6 ± 1,1	0,009
Right hand movement	1,0 ± 0,7	1,0 ± 0,8	0,838	2,2 ± 0,8	1,3 ± 0,8	0,002
Left hand movement	1,3 ± 0,9	0,9 ± 0,7	0,093	2,3 ± 0,9	1,4 ± 0,9	0,003
Right hand pronation	1,3 ± 0,7	1,1 ± 0,6	0,235	2,3 ± 0,8	1,6 ± 0,8	0,005
Left hand pronation	1,5 ± 0,9	1,3 ± 0,7	0,398	2,6 ± 0,9	1,7 ± 0,9	0,005
Right toes	1,0 ± 0,7	1,0 ± 0,8	1	2,0 ± 0,8	1,3 ± 0,6	0,002
Left toes	1,4 ± 0,9	1,4 ± 0,8	0,859	2,2 ± 1,1	1,6 ± 0,9	0,017
RLL agility	0,7 ± 0,6	0,6 ± 0,8	0,657	2,0 ± 0,7	0,9 ± 0,8	<0,001
LLL agility	1,2 ± 0,9	0,8 ± 0,6	0,067	2,1 ± 0,9	1,1 ± 0,9	0,003
Get up	0,2 ± 0,4	0,1 ± 0,2	0,371	1,1 ± 0,7	0,6 ± 0,5	0,022
Walk	0,8 ± 0,6	0,7 ± 0,6	0,61	1,8 ± 0,8	1,1 ± 0,6	0,009
Freezing	0,2 ± 0,5	0,2 ± 0,5	1	1,2 ± 1,3	0,4 ± 0,7	0,008
Postural stability	0,6 ± 0,6	0,3 ± 0,6	0,069	1,4 ± 0,9	0,6 ± 0,9	0,002
Posture	0,5 ± 0,6	0,4 ± 0,5	0,281	1,3 ± 0,6	0,7 ± 0,6	0,006
Global movement	1,1 ± 0,7	1,1 ± 0,6	0,824	2,5 ± 0,6	1,6 ± 0,6	<0,001
Right hand postural tremor	0,4 ± 0,7	0,2 ± 0,4	0,402	1,1 ± 1,2	0,2 ± 0,4	0,01
Left hand postural tremor	0,5 ± 0,8	0,2 ± 0,5	0,059	1,1 ± 1,1	0,1 ± 0,2	0,002
Right hand Kinetic tremor	0,2 ± 0,7	0 ± 0	0,371	0,7 ± 1,1	0,1 ± 0,2	0,028
Left hand Kinetic tremor	0,3 ± 0,5	0,1 ± 0,2	0,059	0,7 ± 1,0	0,1 ± 0,2	0,014
RUL rest tremor amplitude	0,5 ± 1,1	0,1 ± 0,2	0,093	1,5 ± 1,4	0,3 ± 0,5	0,004
LUL rest tremor amplitude	0,7 ± 0,9	0,1 ± 0,3	0,014	1,7 ± 1,3	0,4 ± 0,8	0,001
RLL rest tremor amplitude	0,2 ± 0,5	0,1 ± 0,2	0,361	1,1 ± 1,1	0,3 ± 0,6	0,019
	0,4 ± 0,8	0,1 ± 0,3	0,116	1,2 ± 1,3	0,4 ± 0,9	0,019

Table 2 (*continued*)

Period	*ON*-medication			*OFF*-medication		
Parameters (mean ± SD)	Baseline	12 months	p-value[1]	Baseline	12 months	p-value[1]
LLL rest tremor amplitude						
Lips rest tremor amplitude	0,3 ± 0,9	0,1 ± 0,2	0,371	0,5 ± 0,8	0,2 ± 0,4	0,116
Tremor persistence rest	0,7 ± 1,0	0,3 ± 0,9	0,169	2,3 ± 1,6	0,6 ± 0,9	0,001
Total	26,1 ± 11,7	18,1 ± 10,0	**0,001**	57,4 ± 16,3	28,6 ± 10,9	**<0,001**

Legend: [1] paired Wilcoxon significance level; SD: standard deviation; RUL: right upper limb; LUL: left upper limb; RLL: right lower limb; LLL: left lower limb.

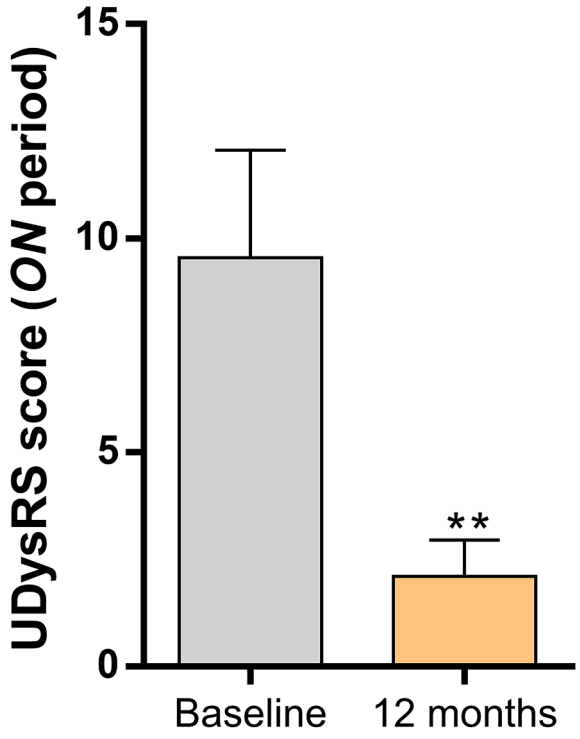

Fig. 2. Scores on the unified scale for the assessment of dyskinesia (UDysRS) during the *on*-medication period obtained preoperatively (baseline) and post-operatively (12 months). ** $p < 0.01$, paired Wilcoxon test.

domains did not change considerably or showed a slight reduction, but without significant differences, as shown in Fig. 3b.

Concerning the LED in the pre and postoperative periods, there was a significant LED reduction of approximately 40% ($p < 0.001$) 12 months after the surgical procedure (Fig. 4), showing a positive impact of DBS on reducing medication therapy.

Finally, using Spearman's correlation, no correlation was identified between baseline factors and the score on the PDQ-39 scale 12 months after DBS implantation (Table 4).

4. Discussion

Considering the high prevalence of PD and the fact that this disease has no cure, well-established interventions that assist in the well-being of patients with PD are needed [41]. DBS is a surgical technique that has provided many benefits to patients in moderate and advanced PD stages [14]. Despite the large number of studies published at an

Table 3
Distribution of patients according to the Hoehn and Yahr scale – on and off-medication periods.

HY stages	*on*-medication period		*off*-medication period	
	Baseline	12 months	Baseline	12 months
1	0 (0%)	2 (10%)	0 (0%)	0 (0%)
1.5	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2	14 (70%)	13 (65%)	2 (10%)	14 (70%)
2.5	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3	6 (30%)	5 (25%)	15 (75%)	6 (30%)
4	0 (0%)	0 (0%)	2 (10%)	0 (0%)
5	0 (0%)	0 (0%)	1 (5%)	0 (0%)
Mean ± SD	2.3 ± 0.5	2.2. ± 0.6	3.1 ± 0.6	2.3 ± 0.5
Mín.–Max.	2–3	1 – 3	2–5	2 – 3
Median	2	2	3	2
p – value[1]	0.525	< 0.001		

Legend: [1] paired Wilcoxon significance level; SD: standard deviation; HY: Hoehn and Yahr; SD: standard deviation.

international level [5,20,21,26,42], data related to this technique are scarce in the Brazilian medical literature [43,44], and it is necessary for a better understanding of the effects of this surgical procedure on several parameters related to motor functions and patients' quality of life. Because of failures and damages resulting from the prolonged use of medications by patients with PD, DBS is an option of considerable importance to relieve symptoms and provide a better quality of life.

Several scales and questionnaires are used to assess the progression of PD. The first scale developed to classify the disability level in PD patients and, consequently, the severity of the disease was the Hoehn and Yahr scale [13]. Before the procedure, the patients presented moderate bilateral disease with some postural instability and the ability to live independently, and after 12 months, they were classified in the stage of bilateral disease without balance deficit. The changes observed after 12 months of the procedure suggest that the surgical procedure had a positive influence on reducing the patient's incapacity in the absence of medication, leading to an improvement in the mentioned scale. Our result is in line with previous works in the literature, as demonstrated by the study by Kahn and collaborators [45], that evaluated 15 patients in stages 4 and 5 of this same scale, retrospectively, and demonstrated a significant improvement in the disability level after an average of 44 months.

Changes in motor capacity, characteristic of PD, including muscle stiffness, involuntary tremor, and bradykinesia [7–9], gradually and significantly compromise patients' independence, autonomy, and well-being. The present study found a decrease in the total score of the UPDRS-III scale relative to the preoperative period, both in the on and off-medication periods, this decrease being more significant in the off-medication period. Similarly, Patel et al. (2003) [46] also found an evident reduction in both periods: 61% in the off-medication period and 40% in the on-medication period, in a study with 16 PD patients and with a 12-month follow-up period. However, other observational studies showed a decrease similar to that found in our study in the off-medication scores concerning the preoperative, but the on-medication period did not register a significant difference [47,48]. These data show that DBS in the subthalamic nucleus has a vital improvement factor in motor symptoms, especially in the off-medication period.

DBS has consistently shown its role in reducing the total scores of the UPDRS-III scale and, consequently, in patients' motor symptoms with only 6 months of follow-up [19,25,26]. Our study showed a significant decrease in the parameters of stiffness in the four limbs and the tremor's amplitude at the rest of the left upper limb in the *on*-medication period. Except for speech and amplitude of the tremor at rest on the lip, all parameters in the *off*-medication period showed a significant decrease. Literature data demonstrate that speech does not generally show

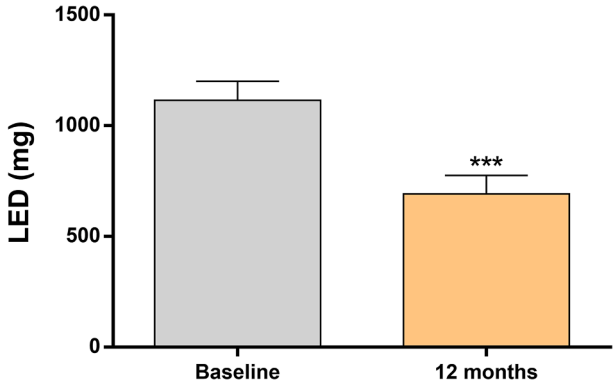

Fig. 4. Daily Levodopa Equivalent Dose (LED) calculated before and 12 months after the procedure. *** $p < 0.001$.

Table 4
Association of baseline factors with score in the PDQ-39 scale after 12 months.

Baseline item	r	95% IC	*P-value*
Age	−0.278	−0.649 – 0.200	0.237
Disease duration	0.118	−0.355 – 0.543	0.621
Hoehn and Yahr stage – *on*	−0.360	−0.699 – 0.113	0.119
Hoehn and Yahr stage – *off*	0.039	−0.422 – 0.484	0.870
UDPRS III – *on*	0.176	−0.302 – 0.583	0.458
UDPRS III – *off*	0.087	−0.382 – 0.520	0.716
UDysRs – *on*	−0.204	−0.602 – 0.276	0.389
PDQ-39	0.183	−0.295 – 0.588	0.439
LED	0.243	−0.237 – 0.628	0.302

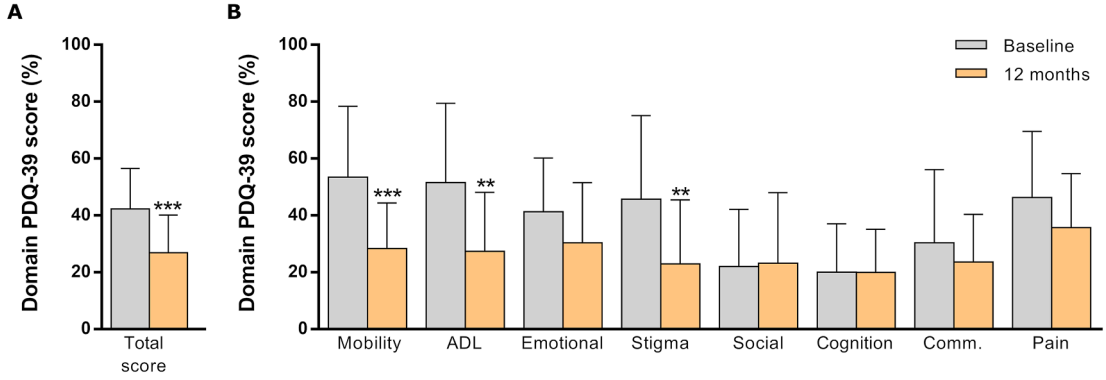

Fig. 3. Scores on PDQ-39 scale (quality of life) (A) Total scores on PDQ-39 scale (B) Domains scores on PDQ-39 scales. The data correspond to the mean ± standard deviation (SD) obtained preoperatively (baseline) and *on*-DBS postoperatively (12 months). ADL: Activity of daily living; Comm.: Communication. ** $p < 0.01$, *** $p < 0.001$, paired Wilcoxon test.

significant improvement after DBS. A retrospective study with 85 patients submitted to DBS showed that after evaluating the patients using the UPDRS-III scale, there was no change in the parameters of speech, cognitive function, and hallucinations [49]. Rodriguez-Oroz et al. (2012) [50], in a review of long-term outcomes of studies with follow-up of at least 5 years, showed that out of 9 studies with an *off*-period analysis, 6 did not find improvement in the speech parameter.

Dyskinesias are also motor symptoms influenced by DBS. In this study, we demonstrated this influence from the significant decrease in dyskinesias 12 months after the surgical procedure in the on-medication period. Lagrange et al. (2002) [47], evaluated on-dyskinesias in the same follow-up period and with 60 patients and showed decreased scores. Dyskinesias can also occur during off-medication periods when dopamine levels are low, and their clinical presentation is predominantly dystonic. Off-medication dystonia is seen in approximately 20–30% of PD patients and is typically seen early in the morning before L-DOPA first dose. Therefore, longer-acting dopaminergic agonists and controlled release of L-DOPA can be used to prevent a drop in dopamine levels during the night and thus prevent morning dystonia [51]. In this study, we showed that 2 out of 20 participants (10%) had dyskinesias during the off-medication period, whereas in one participant the DBS reduced dystonia, from 5 to 0 in UDysRS scale, while in another one it remained unchanged, in the pre and postoperative period, with score 2 obtained in both moments.

Not only motor symptoms but non-motor symptoms are also quite common and disabling in patients with PD. Depression, disturbances of the sleep-wake cycle, cognitive impairments involving memory, dementia and hallucinations, anxiety, mood disorders, and pain are quite common in patients with PD, and all these symptoms are associated with a significant reduction in the patient's quality of life [10–12,31]. From the application of the PDQ-39 questionnaire, we observed improvement in the domains of mobility, the activity of daily living, and stigma. Similarly, other studies found a significant improvement in patients' quality of life after DBS, especially concerning mobility [20,27,28,52]. These results corroborate those obtained in the present study, making it possible to suggest the positive influence of the surgical procedure on the quality of life of the individuals evaluated.

In our study, it was not possible to observe a correlation between improvement of quality of life and the parameters assessed in pre and postoperative periods. Indeed, there is no consensus regarding the factors that influence the quality of life of patients with PD after DBS, suggesting that the determination of these parameters may be individual and heterogeneous [53].

Regarding the equivalent dose of levodopa (LED), it is argued that the beginning of motor symptoms is related to the duration of PD and the dose of L-DOPA administered and not to the time of exposure to the drug [54,55]. However, a recent meta-analysis showed no difference was observed in dyskinesias or activities of daily life changes between high or low LED reduction after DBS [56]. It is possible to observe a variation between the LED reductions found in the literature. We found a significant reduction of about 40% concerning the dose used in the preoperative period, demonstrating the action of the surgical procedure in the control of symptoms, directly interfering in the need for doses of drug therapy. Rodriguez et al. (2005) [50] observed a similar reduction in LED of approximately 35% in a study conducted with 49 patients and followed up for 4 years. In a study conducted by Mossner et al. (2019) [57], a LED reduction of approximately 50% was observed in patients after the DBS procedure. Simonin et al. (2009) [58] observed a reduction of 43% in LED after 1 year of the procedure in a study conducted with 33 patients. A prospective study that evaluated the effects of DBS in 41 patients with PD for 12 months reported a reduction of 59.7% in LED after the surgical procedure [30]. Randomized studies demonstrated a reduction of 50.8% [20] and 23.1% [27] in LED compared to the score of 6 months earlier.

There is a wide variation between clinical studies regarding scores obtained in the motor function scales, quality of life, and the levodopa reduction. However, in a review performed by Benabid et al. (2009), it is possible to observe that the improvements are observed globally, reinforcing the effectiveness of DBS [59].

Our study corroborates previous findings and provides data from Brazilian patients, which are scarce in the literature. Besides that, the analyzes included the UPDRS, UDysRS, Hoehn and Yahr, PDQ-39, and LED assessments for patients with PD that had DBS, data that are also poorly explored in the literature together.

As a limitation of this study, the sample size of 20 participants may have influenced the results obtained and/or the absence of a significant difference between the periods (on and off; pre and postoperative). However, it is possible to observe studies with smaller samples that obtained similar results [46]. We emphasize that it is a restricted population since it is composed only of patients treated and monitored in one hospital environment. It is important to note that, despite the small sample, the heterogeneity of the individuals included, and the 12-month follow-up, it was already possible to observe significant differences within very robust confidence intervals. Another limitation is that we did not implement a patient's activity daily record to quantify the reduction of off-medication periods throughout the day. It is known that this reduction in off-medication periods is one of the most related factors to improve the functionality of patients [60]. Also, we did not use an assessment scale for non-motor symptoms whose expected reduction after surgical treatment should impact the patients' quality of life.

5. Conclusion

Bilateral DBS of the subthalamic nucleus in patients with PD promoted not only an improvement in motor function in the *on* and *off*-medication period 12 months after DBS implantation but also an improvement in the disease stage in the *off*-medication period, the quality of life self-reported by the patient and a significant reduction in the dose of L-DOPA, compared with preoperative parameters.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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