

## ORIGINAL ARTICLE

# Effect of the combination pallidotomy-subthalamotomy performed in opposite cerebral hemispheres for the treatment of motor signs in Parkinson's disease



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## KEYWORDS

Parkinson's disease;  
Pallidotomy;  
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Functional  
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## Abstract

**Introduction:** Functional Neurosurgery constitutes a therapeutic alternative for patients with Parkinson's Disease (PD). It is known that both bilateral subthalamotomy and bilateral pallidotomy cause neurological complications, so in ablative techniques a bilateral approach to the GPi is not recommended in PD and caution is suggested with the indication of bilateral subthalamotomy. Our group has refined the surgical technique for the ablation of the subthalamic nucleus seeking to reduce the appearance of dyskinesias induced by surgery and obtain a better therapeutic effect, so the approach to the NST in a second surgical procedure in the opposite

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hemisphere to the one performed previously pallidotomy, would avoid the complications derived from bilateral pallidotomy and can be a safe alternative for patients even when they present symptoms of dyskinesias. We set out to evaluate the effect and safety of the combination of GPi and NST lesion in opposite cerebral hemispheres in PD patients.

**Method:** A retrospective study was carried out that included all patients operated on at the CIREN in a period of 22 years, who underwent a pallidotomy contralateral to the most affected hemibody; followed by a subthalamotomy of the opposite hemisphere in a second surgical procedure. The effect on the neurological condition was evaluated using section III of the MDS-UPDRS scale. Safety was evaluated according to the adverse effects scale and the Clavien and Dindo scale.

**Results:** Both surgical interventions had a positive impact on the patients' pharmacological treatment, significantly reducing the doses of L-dopa. A significant improvement was observed in the motor condition of the patients in relation to dyskinesias, as well as rigidity, bradykinesia and tremor.

**Conclusions:** The pallidotomy/subthalamotomy combination showed to be an effective alternative for the treatment of complicated PD, capable of allowing better motor control and a reduction in the dose of L-Dopa with a low rate of complications; it also allows to avoid complications derived from bilateral pallidotomy and subthalamotomy, proving to be a safe alternative for patients even when they present symptoms of dyskinesias.

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## PALABRAS CLAVE

Enfermedad de Parkinson;  
Palidotomía;  
Subtalamotoía;  
Neurocirugía funcional

## Efecto de la combinación Palidotomía-Subtalamotoía realizada en hemisferios cerebrales opuestos para el tratamiento de los signos motores en la Enfermedad de Parkinson

### Resumen

**Introducción:** La Cirugía Funcional constituye una alternativa terapéutica para los pacientes con Enfermedad de Parkinson (EP). Es conocido que tanto la subtalamotoía como la palidotomía bilaterales provocan complicaciones neurológicas, por lo que en las técnicas ablativas no resulta recomendable el abordaje bilateral del GPi en la EP y se sugiere tener precaución con la indicación de la subtalamotoía bilateral. Nuestro grupo ha perfeccionado la técnica quirúrgica para la ablación del núcleo subtalámico buscando disminuir la aparición de las discinesias inducidas por la cirugía y obtener mejor efecto terapéutico, por lo que el abordaje del NST en un segundo tiempo quirúrgico en el hemisferio opuesto al que se realizó previamente la palidotomía, evitaría las complicaciones derivadas de la palidotomía bilateral y puede ser una alternativa segura para los pacientes aun cuando estos presenten cuadros de discinesias. Nos propusimos evaluar el efecto y la seguridad de la combinación de la lesión del GPi y del NST en hemisferios cerebrales opuestos en pacientes con EP.

**Método:** Se realizó un estudio retrospectivo que incluyó a todos los pacientes operados en el CIREN en un periodo de 22 años, a los que se les realizó una palidotomía contralateral al hemicuerpo más afectado; seguida de una subtalamotoía del hemisferio opuesto en un segundo tiempo quirúrgico. El efecto sobre la condición neurológica fue evaluado mediante la sección III de la escala de MDS-UPDRS. Se evaluó la seguridad según escala de efectos adversos y escala de Clavien y Dindo.

**Resultados:** Ambas intervenciones quirúrgicas tuvieron un impacto positivo en el tratamiento farmacológico de los pacientes reduciéndose significativamente las dosis de L-dopa. Se observó una mejoría significativa en la condición motora de los pacientes en relación a las discinesias, así como a la rigidez, la bradicinesia y el temblor.

**Conclusiones:** La combinación palidotomía/subtalamotoía mostró ser una alternativa efectiva para el tratamiento de la EP complicada, capaz de permitir un mejor control motor y una reducción de la dosis de L-Dopa con una baja tasa de complicaciones; permitiendo además evitar las complicaciones derivadas de la palidotomía y de la subtalamotoía bilaterales, demostrando ser una alternativa segura para los pacientes aun cuando estos presenten cuadros de discinesias.

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## Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease globally, after Alzheimer disease.<sup>1–3</sup> It is characterised by non-motor manifestations<sup>4,5</sup> and motor symptoms of unilateral onset with asymmetrical, bilateral progression, with greater involvement of the side affected at onset.<sup>6,7</sup> At early stages, signs and symptoms are largely alleviated by levodopa (L-DOPA), which constitutes the most effective symptomatic treatment.<sup>8,9</sup> However, with long-term use of this treatment, patients begin to show motor complications including fluctuations and dyskinesia, as well as gait, postural, and balance alterations, which dramatically affect their quality of life.<sup>10–13</sup>

Functional surgery currently represents a treatment option for patients with PD and a crucial tool for controlling motor complications that do not respond adequately to pharmacological therapies.<sup>14,15</sup>

The bilateral progression of motor signs and symptoms justifies the need for treatment in both hemispheres. Deep brain stimulation currently represents the surgical technique of choice, as bilateral stimulator implantation can safely be performed in a single procedure, and is associated with a significantly greater motor improvement than that observed with unilateral procedures.<sup>16–20</sup> However, the procedure is restricted to countries with access to the technology; other limitations are its high cost, complexity, and the existence of complications associated with electrode implantation.<sup>21</sup> Therefore, ablative techniques remain a treatment alternative today.<sup>22</sup>

In recent years, the subthalamic nucleus (STN) and internal globus pallidus (GPi) have been the 2 surgical targets of choice to improve motor status in advanced PD.<sup>23,24</sup> Selection of a surgical target should account for the predominant symptoms in each patient and the more severely affected hemibody (generally the side affected at disease onset). Numerous studies in the literature report the use of subthalamotomy in patients with predominant rigid-akinetic syndrome<sup>25,26</sup>; however, the majority of researchers are hesitant to perform the procedure in patients with severe dyskinesia.<sup>27–29</sup> On the other hand, the GPi is targeted in the first procedure in patients with motor symptoms secondary to dopaminergic medication, such as dyskinesias.<sup>30,31</sup>

Both bilateral subthalamotomy and deep brain stimulation of the bilateral STN have been employed with relative success in patients with PD.<sup>32,33</sup> Nonetheless, some studies in the literature report the onset of complications after bilateral subthalamotomy,<sup>26,34</sup> such as the development of dyskinesia or hemichorea-ballism after the second procedure; cases have even been reported of speech disorders (volume)<sup>35,36</sup> and impaired cognitive function, although the reported incidence rates are low.<sup>37</sup> Bilateral pallidotomy is also known to cause severe complications, mainly affecting speech and cognitive function.<sup>38,39</sup> As a result, bilateral GPi ablation has been ruled out in PD, and is preferred for the treatment of dystonia, chorea, and other dyskinesias.<sup>40–43</sup>

In the light of these 2 observations, bilateral pallidotomy is not recommended in PD, and caution should be exercised when indicating bilateral subthalamotomy. Our study group has worked to improve functional surgery approaches, refining the surgical technique for STN ablation, seeking to improve treatment outcomes and reduce the appearance of surgery-induced dyskinesia.<sup>44,45</sup> Thus, ablation of the STN in a second procedure, contralateral to the initial pallidotomy procedure, would avoid the complications related to bilateral pallidotomy and may constitute a safe alternative for patients, even among those presenting dyskinesia. Based on the arguments above and the current lack of evidence on the subject, the present study aims to evaluate the safety and efficacy of the combination of pallidotomy and subthalamotomy in opposite cerebral hemispheres.

## Patients and methods

We conducted a retrospective, longitudinal, descriptive-correlational study. The study sample was made up of all patients diagnosed with idiopathic PD according to the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) criteria<sup>46</sup> and treated with an initial pallidotomy and subsequently with contralateral subthalamotomy in a second surgical procedure, at the neurosurgery department of the International Center for Neurological Restoration (CIREN; Havana, Cuba), over a 22-year period.

Inclusion criteria:

- 1 Patients diagnosed with idiopathic PD according to the UKPDSBB criteria and treated with bilateral functional surgery.
- 2 Patients undergoing pallidotomy in one hemisphere and subthalamotomy in the other, in separate procedures, at the neurosurgery department of CIREN.

Exclusion criteria:

- 1 Patients also undergoing ablation of the basal ganglia, such as thalamotomy of the ventral intermediate nucleus.
- 2 Patients undergoing subthalamotomy in the first procedure.

## Description of the surgical technique

The stereotactic frame (ESTEREOFLEX, Tecnosuma; Havana, Cuba) was positioned under antiseptic conditions and local anaesthesia, achieving the greatest possible parallelism between the plane of the frame and the intercommissural plane (anterior and posterior commissure). This was achieved by positioning the frame perpendicular to the midsagittal plane, avoiding coronal tilt of the frame and attempting to achieve a sagittal tilt of the ring at an angle of 10°–15° between this and the imaginary orbitomeatal line.

Stereotactic CT images were taken after fixing the stereotactic localiser on the frame and attaching the frame to the CT table. The CT study used 1 mm axial slices, with intravenous iodinated contrast. Axial slices were taken perpendicular to the bed, with no gantry tilt; slices were 1 mm thick with no overlap, a 250 mm field of view, and a matrix of 512 × 512. Studies were performed in SOMATOM Sensation Cardiac 64 and SOMATOM Definition 128 CT scanners (Siemens; Erlangen, Germany). Images were exported to a personal computer located in the operating theatre.

Coordinates of and tracks towards the therapeutic target were planned using the STASSIS surgical planning system (CIREN; Havana, Cuba).<sup>47,48</sup> The anterior and posterior commissures (AC and PC, respectively) were identified, and the anatomical plane with the best definition of both structures was located. If the AC and PC did not coincide on a single axial slice, images were reconstructed. Having located and marked the AC and PC, we overlaid scanned slices from the Schaltenbrand and Wahren (SW) stereotactic atlas on the CT images, scaling them with automatic adjustment to the patient's intercommissural distance, and defining the borders of the ventricles, thalamo-capsular border, and the pallido-capsular border.

The surgical target and the track towards it were defined according to the values presented in Table 1. The position of the target was established in relation to the midcommissural point (MCP). The 2 degrees of freedom for defining the track were (alpha) with respect to the midsagittal plane (to avoid the ventricular system) and (beta) the anteroposterior angle with respect to the horizontal intercommissural plane. The initial coordinates for identifying the STN were, from the MCP: 3 mm posterior, 3 mm inferior, and 11–12 mm lateral. Semi-microelectrode tracks were planned and made with a parasagittal (alpha) angle of 5–25 degrees<sup>45</sup> and an angle of 60–65 degrees anteroposterior (beta) to the AC-PC plane.<sup>49</sup>

**Table 1** Approach coordinates.

| Surgical target | Position relative to MCP |                           |                        | Approach angle       |                         |
|-----------------|--------------------------|---------------------------|------------------------|----------------------|-------------------------|
|                 | Latero-lateral (x-axis)  | Postero-anterior (y-axis) | Dorso-ventral (z-axis) | Parasagittal (alpha) | Antero-posterior (beta) |
| STN             | ± 11–12 mm               | –3 mm                     | +3 mm                  | 5–25°                | 60–65°                  |
| GPI             | ± 19 to –20 mm           | +3 mm                     | +3 mm                  | 5°–15°               | 50°–55°                 |

GPI: internal globus pallidus; MCP: midcommissural point; STN: subthalamic nucleus.

Multi-unit recording to locate the target was performed by inserting a cannula with a concentric bipolar semi-microelectrode (UK 100, Unique Medical Co. Ltd.; Tokyo, Japan; diameter of 0.4 mm, and impedance of 100 K $\Omega$  or equivalent). Multi-unit neuronal activity was recorded and visualised with the Neurosurgical Deep Recording System (NDRS; CIREN; Havana, Cuba) digital recording and processing tool.<sup>50,51</sup> We advanced cautiously with visual and auditory monitoring of multi-unit electrical activity, from a point 20 mm superior to the theoretical target, using the micromanipulator to attempt to identify the different structures before arrival at the target. Subsequent tracks were made to locate the border between the white and grey matter and to establish the somatotopic representation of the target selected.

### Identification of the internal globus pallidus

On the advance along each track, recording was performed every 1 mm in the vicinity of the target, and ended when the optic tract was identified or when a distance 5 mm below the nucleus was reached. According to results from the first track, parallel tracks are made at a suitable separation, until the sequence of structures present is identified (lateral pallidus, medial pallidus, substantia nigra pars reticulata, or optic tract). After this, translations were posterolateral or anteromedial at a 45° angle with respect to the midline, until the most posterior and most lateral segments of the nucleus were identified. Electrical stimulation along some tracks in the inferior half of the medial pallidus nucleus enabled assessment of the distance to the internal capsule. During multi-unit recording, the GPI was identified according to the electrical activity observed, considering variations in amplitude; this enabled identification of adjacent structures congruent with the track, according to the angle of approach to the target.

### Microstimulation

Microstimulation was performed with the same electrode as recording, in order to identify motor pathways from the cerebral cortex.

### Macrostimulation

Macrostimulation was performed with an ELEKTA lesion generator, with 4 mm active-tip electrodes. Stimulation parameters were as follows: 60 Hz, with 0.5 ms pulse width in controlled current mode (mA), with a progressive, manual increase from 0 mA to a maximum of 5 mA until adverse effects were observed. The safety threshold is set at 2 mA or higher; for lower values, lesion location is re-evaluated.

### Lesioning of the target area

The final coordinates for establishing the lesion area are fundamentally based on the neurophysiological findings, with minimal corrections in the event that stimulation produces effects suggesting proximity to the internal capsule.

### Identification of the subthalamic nucleus

On the advance along each track, recording was performed every 1 mm in the vicinity of the target, and ended at the end of the area of increased multi-unit activity, with this activity returning to the level of white matter recording, or when we observed a two-thirds drop in integrated electrical activity with respect to the maximum for the nucleus. Parallel tracks were made anterior or posterior to the first to identify the anterior and posterior borders of the nucleus on its antero-posterior axis; based on the best recordings, subsequent translations were made at 45° towards the lateral and posterior extreme of the nucleus. Electrical stimulation was applied along this track from a point located in the superior half of the nucleus; this stimulation is very important in calculating the distance to motor fibres originating in the motor cortex. During multi-unit recording, identification of the STN was based on the following parameters:

- Increased electrical activity, characterised by large discharge amplitude, which is always higher than the activity observed in the thalamus and substantia nigra pars reticulata.
- Sequential recording of the following structures along the electrode track: anterior thalamus or corona radiata, zona incerta, STN, substantia nigra pars reticulata, and white matter.
- Variations in discharge amplitude and in the distance in millimetres of integrated electrical activity were determining factors in mapping the borders of the lesion.

### Microstimulation

Microstimulation was performed with the same electrode as recording, and sought to identify motor pathways from the cerebral cortex.

### Macrostimulation

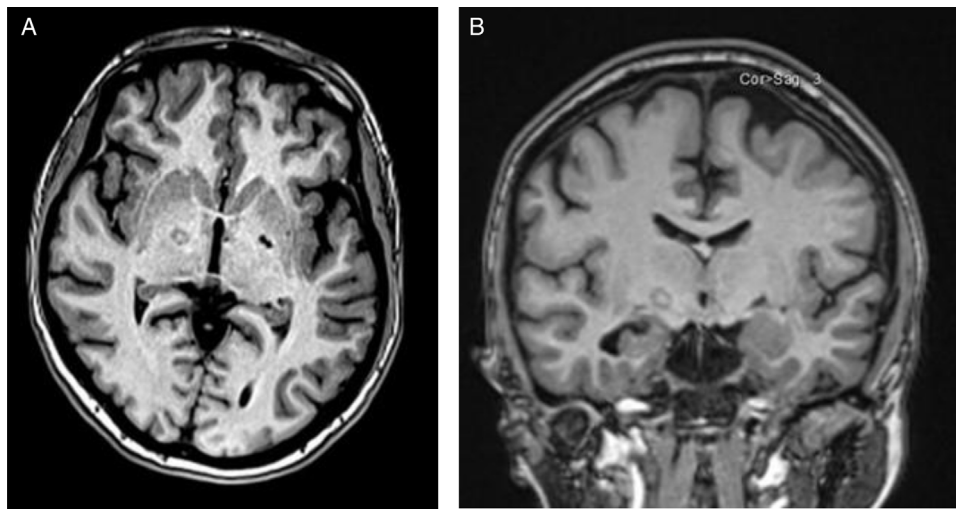
Macrostimulation was conducted with an ELEKTA lesion generator, with 2 mm active-tip electrodes. Stimulation parameters were as follows: 60 Hz, with 0.5 ms pulse width in controlled current mode (mA), with a progressive, manual increase from 0 mA to a maximum of 5 mA until adverse effects were observed. A safety threshold of 2 mA or higher was established; for lower values, lesion location is re-evaluated.

### Lesioning of the target area

The final coordinates for establishing the lesion area are fundamentally based on the neurophysiological findings, with minimal corrections in the event that stimulation produces effects suggesting proximity to the internal capsule.

### Lesioning of the internal globus pallidus

Two radiofrequency lesions were made with a 1.1 mm diameter electrode with a 4 mm active tip, to ablate to the greatest extent



**Figure 1** Postoperative axial (A) and coronal (B) MRI sequences obtained after both surgical procedures (left pallidotomy/right subthalamotomy).

possible the areas with greatest electrical activity. The first lesion was more posterior and lateral, starting at the inferior boundary of the nucleus, 1.5–2 mm from the optic tract. The second lesion was performed 2.5 mm anterior and 2.5 mm medial to the first, following the same targeting strategy. Both lesions were made in the ventral region of the nucleus. Maximum temperature was 70 or 80 °C. A temperature of 80 °C was used when 70 °C did not achieve the desired therapeutic effect.

### Lesioning of the subthalamic nucleus

Two radiofrequency lesions were made with a 1.1 mm diameter electrode with a 2 mm active tip, to ablate to the greatest extent possible the areas with greatest electrical activity. Thus, the lesion extended upwards from the halfway point of the nucleus to 0.5–1 mm beyond its upper border, in the direction of the lesion track. The first lesion was more posterolateral, and the second lesion was performed 2 mm anterior and 2 mm medial to the first. Maximum temperature was 70 or 80 °C. A temperature of 80 °C was used when 70 °C did not achieve the desired therapeutic effect.

This procedure was performed under strict clinical control, with the patient awake, with constant evaluation of positive responses (with rigidity as the baseline situation) and adverse effects (mainly motor). Finally, the lesion was closed by planes, with attention paid to haemostasis.

All patients underwent a postoperative MRI study with a 1.5 T scanner (1.5 T Magnetom Aera, Siemens; Germany) (Fig. 1).

### Motor status assessment

- Motor symptoms were evaluated using section III of the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS).<sup>52</sup>

### Safety assessment

- Safety assessment sought to identify the immediate functional complications associated with the surgical lesion,
- and surgical complications related to the procedure that may occur from the time of stereotactic frame placement, during and after the surgery.<sup>53</sup>

### Data gathering

#### Data gathering procedure

The results of all clinical and instrumental assessments performed were gathered from the NDRS program, the STASSIS program, and patients' clinical records, and compiled in an integrated database designed for the statistical analysis.

#### Data processing and analysis

We conducted a descriptive analysis of each variable included in the assessment scales for each of the response variables, and their behaviour in each patient, in accordance with the variables of interest.

To evaluate the effect of the intervention on patients' neurological condition, the percentage of improvement was calculated.

Comparison of variables before and after the surgical procedure was conducted with the *t* test, whereas correlations were evaluated with the Spearman test.

#### Ethical considerations

Given the characteristics of the research, the informed consent of patients and their family members was not required, as this is a retrospective study based on data gathered from patients' clinical records, with no risk to their privacy. Patients independently consented to undergo the surgical procedure. We present a summary of outcomes in all the patients included.

### Results

Over a period of 22 years, a total of 45 patients underwent pallidotomy in one hemisphere and subthalamotomy in the other. Of these, only 19 patients met the study inclusion criteria. All 19 had been diagnosed with PD according to the UKPDSBB criteria, responded positively to L-DOPA, and presented motor complications. Of the 45 patients undergoing these procedures at the CIREN during the study period, 24 were excluded due to missing data or because the subthalamotomy was performed in the first procedure.

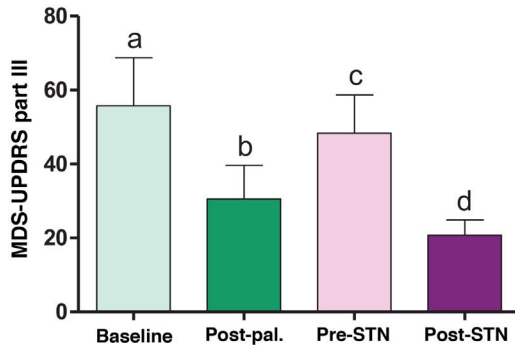
The mean age prior to the pallidotomy was 50 years (range, 32–67). No sex predominance was observed, with a difference of 1 between the number of men and the number of women. The right side of the body was more frequently affected at onset and more severely affected at the time of surgery; thus, the left GPi was



**Table 2** Demographic characteristics of the patient series and disease progression prior to each surgical intervention.

|                                            | Progression before pallidotomy | Progression before subthalamotomy |
|--------------------------------------------|--------------------------------|-----------------------------------|
| Mean age (SD), years                       | 50.42 (9.46)                   | 54.89 (9.75)                      |
| Male/female                                | 8/9                            |                                   |
| Mean disease progression time (SD), years  | 9.53 (3.90)                    | 14.00 (5.08)                      |
| Mean time between surgeries (range), years | —                              | 4.5 (1–10)                        |
| Hemisphere targeted                        | 8 R/11 L                       | 11 R/8 L                          |

L: left; R: right; SD: standard deviation.



**Figure 2** Motor behaviour assessment before and after the surgical interventions. Bars show the mean scores for part III of the Movement Disorders Society-Unified Parkinson's Disease Rating Scale at the different time points. The letters above the bars indicate the presence of significant differences, according to the Wilcoxon test for paired samples: a vs b:  $P = .000132$ ; c vs d:  $P = .000132$ ; b vs c:  $P = .000132$ , a vs c:  $P = .004970$ . MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale; pal.: pallidotomy; STN: subthalamotomy.

targeted in 11 patients and the right in 8. A mean delay of 4.5 years (range, 1–10) between surgeries was observed (Table 2).

All patients treated with pallidotomy-subthalamotomy had advanced PD with a deterioration of their neurological status, as demonstrated by high scores on the MDS-UPDRS motor subscale applied during OFF state, and the presence of motor complications. The mean MDS-UPDRS part III score prior to pallidotomy was 55.78 (range, 26–74), with patients showing the cardinal signs of the disease, which were more severe in the hemibody affected at symptom onset. In a high percentage of patients, the main features of the clinical picture were moderate to severe choreic dyskinesia and motor fluctuations (Table 3).

After pallidotomy but prior to subthalamotomy, rigidity and bradykinesia were the cardinal symptoms most frequently observed (64.70% of the sample). Furthermore, patients displayed neurological deterioration and motor complications (dyskinesia, dystonia, and motor fluctuations), which were more marked in the hemibody ipsilateral to the pallidotomy.

### Effect of surgery on motor behaviour

Patients' motor status was evaluated with the MDS-UPDRS part III. Regarding the surgical target, thermocoagulation lesions both to the GPi (pallidotomy) and to the STN (subthalamotomy) had significant effects on patients' motor performance (Table 4) (Fig. 2).

After pallidotomy, 100% of patients displayed a significant improvement in motor status (Fig. 2) and a decrease in the frequency and severity of dyskinesia.

However, their neurological motor status did deteriorate over time. Whereas the pre-subthalamotomy assessment showed significantly lower motor scores on the MDS-UPDRS part III with respect to the pre-pallidotomy assessment ( $P = .004970$ ;  $t = 21.00000$ ), these values were significantly higher than those observed immediately after the first intervention (pallidotomy) ( $P = .000132$ ;  $t = 0.00000$ ) (Fig. 2).

After the second intervention (subthalamotomy), all patients displayed a significant improvement in motor capacity, which was greater than that observed after the first procedure (Fig. 2).

The first intervention (pallidotomy) was performed in the hemisphere contralateral to the more severely affected hemibody. Before surgery, patients showed significantly greater rigidity and bradykinesia in one hemibody than in the other (Mann–Whitney U test: rigidity,  $U = 67.0$ ,  $P = .0009$ ; bradykinesia,  $U = 72.0$ ,  $P = .0015$ ). Subsequent to pallidotomy, a significant improvement in motor symptoms was observed in the contralesional hemibody (Wilcoxon test for paired samples: rigidity,  $Z = 3.823$ ,  $P = .0001$ ; bradykinesia,  $Z = 3.723$ ,  $P = .0001$ ; tremor,  $Z = 3.516$ ,  $P = .0001$ ; axial symptoms,  $Z = 3.823$ ,  $P = .0001$ ) (Fig. 3).

Subthalamotomy was performed in the opposite hemisphere to pallidotomy; this important detail should be considered when observing and interpreting the figures. Although as a consequence of the progression of the disease, patients showed motor deterioration with respect to the post-pallidotomy assessment, the hemibody contralateral to this procedure continued to show significantly less rigidity, bradykinesia, and tremor than the other hemibody (Mann–Whitney U test: rigidity,  $U = 34.0$ ,  $P = .00001$ ; bradykinesia,  $U = 48.5$ ,  $P = .0001$ ; tremor,  $U = 110.0$ ,  $P = .039$ ). After subthalamotomy, a significant improvement in motor symptoms was observed, which was more marked in the contralesional hemibody (Wilcoxon test for paired samples: rigidity,  $Z = 3.823$ ,  $P = .0001$ ; bradykinesia,  $Z = 3.823$ ,  $P = .0001$ ; tremor,  $Z = 3.295$ ,  $P = .0009$ ; axial symptoms,  $Z = 3.823$ ,  $P = .000132$ ) (Fig. 4).

Unlike pallidotomy, subthalamotomy induced a significant improvement in bradykinesia in the ipsilesional hemibody (Wilcoxon test for paired samples: bradykinesia,  $Z = 2.022$ ,  $P = .04$ ).

### Effects of surgery on daily levodopa dose

Both surgical interventions had a positive impact on patients' pharmacological treatment. The first procedure (pallidotomy) was associated with a clinical improvement in patients, with a significant decrease in the daily levodopa doses required ( $P = .003360$ ;  $t = 3.376767$ ). Dopaminergic medication doses could be reduced in 14/19 patients. Although the delay between surgical interventions was variable, and L-DOPA doses were lower at the time of the second intervention (subthalamotomy) than at the time of the first assessment (Table 5), a significant increase in L-DOPA consumption was observed with respect to the values recorded a year after

**Table 3** Motor complications in patient clinical assessments.

| Motor complications | Pre-pallidotomy (No. patients) | %     | Pre-subthalamotomy (No. patients) | %     |
|---------------------|--------------------------------|-------|-----------------------------------|-------|
| Choreic dyskinesia  | 14                             | 73.68 | 4                                 | 21.05 |
| Dystonia            | 5                              | 26.31 | 3                                 | 15.78 |
| Motor fluctuations  | 11                             | 57.89 | 4                                 | 21.05 |

Source: data collection sheet.

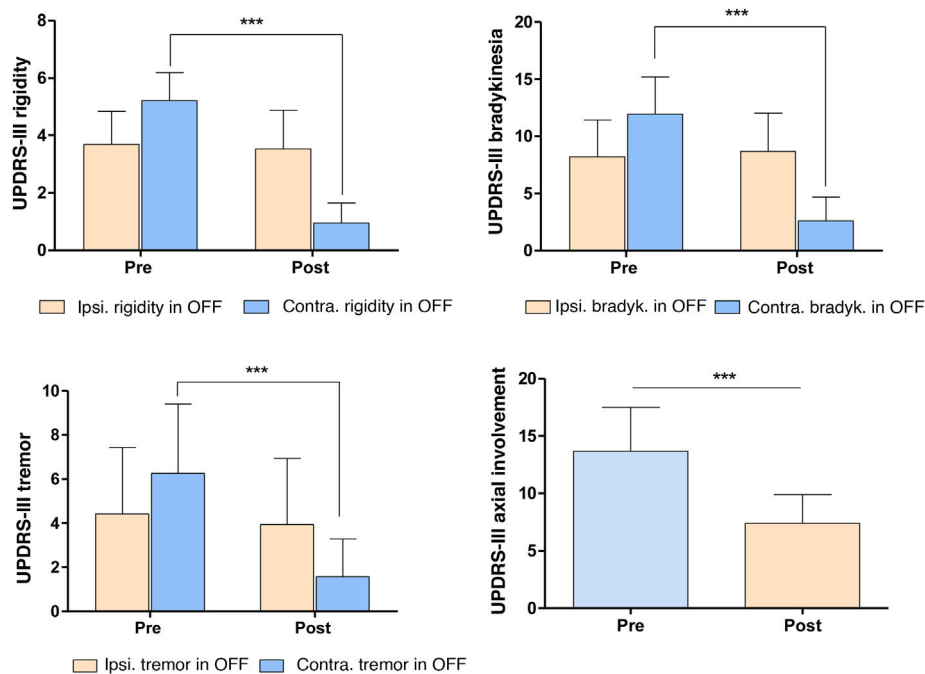
**Table 4** Changes in motor behaviour after surgery.

| UPDRS          | Preoperative mean (SD) | Postoperative mean (SD)   | % improvement mean (SD) |
|----------------|------------------------|---------------------------|-------------------------|
| Pallidotomy    | 53.5 (12.99)           | 28.14 (8.68) <sup>a</sup> | 47.66% (8.92%)          |
| Subthalamotomy | 47.21 (8.98)           | 20.64 (4.20) <sup>a</sup> | 55.88 (6.38%)           |

Source: data collection sheet.

 $P < .0001$ . Dependent samples *t* test.

SD: standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale.

<sup>a</sup> Statistically significant difference. Preoperative vs postoperative values.**Figure 3** Changes in the cardinal signs of Parkinson's disease after pallidotomy. The bar charts show the effect of pallidotomy on the cardinal signs of the disease in both hemibodies, as measured with part III of the Movement Disorders Society-Unified Parkinson's Disease Rating Scale. Mann–Whitney U test and Wilcoxon test for paired samples:  $P < .001$ .

Bradyk.: bradykinesia; contra.: contralateral; ipsi.: ipsilateral; UPDRS: Unified Parkinson's Disease Rating Scale.

pallidotomy ( $P = .045951$ ;  $t = -2.14385$ ). After the second procedure, it was possible to reduce the L-DOPA dose in 17 patients (88.24%). In addition to the greater number of patients whose doses were reduced after subthalamotomy, we also observed a greater reduction in dose per patient with respect to the post-pallidotomy assessment (Table 5).

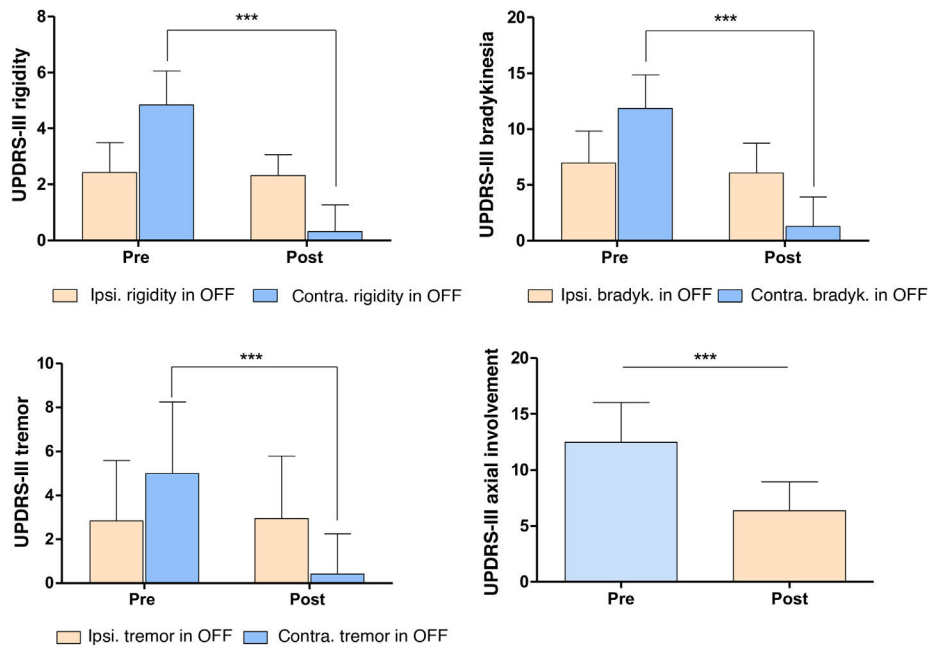
### Peri- and postoperative complications

A total of 38 surgical interventions were performed in 19 patients (19 pallidotomies and 19 subthalamotomies). Life-threatening surgical complications (unrelated to the ablative lesion) were recorded

in 2 patients (5.26% of the 38 procedures): intraparenchymal haemorrhages in both cases. Another 2 cases were recorded of infections of the surgical wound (5.26%); thus, the total rate of surgical complications (unrelated to the ablative lesion) was 10.52% (Table 6).

A further 2 cases were reported of complications related to the ablative lesion. Both patients presented dyskinesia induced by the subthalamotomy. Dyskinesia was mild and transient, and resolved within 2 months after surgery in both cases.

Fig. 5 shows the number of recording tracks made during the surgical interventions to map the target nucleus and establish the lesion zone. Fig. 5A shows the recording tracks made during



**Figure 4** Changes in the cardinal signs of Parkinson's disease after subthalamotomy. The bar charts show the effect of subthalamotomy on the cardinal signs of the disease in both hemibodies, as measured with part III of the Movement Disorders Society-Unified Parkinson's Disease Rating Scale. Mann–Whitney U test and Wilcoxon test for paired samples:  $P < .001$ . Bradyk.: bradykinesia; contra.: contralateral; ipsi.: ipsilateral; UPDRS: Unified Parkinson's Disease Rating Scale.

**Table 5** Change in levodopa dose after the surgical interventions.

| Surgery                                      | Preoperative   | Pallidotomy    | Pre-subthalamotomy | Pallidotomy/subthalamotomy |
|----------------------------------------------|----------------|----------------|--------------------|----------------------------|
| Mean L-DOPA dose (SD), mg                    | 889.47 (249.2) | 681.58 (163.5) | 831.25 (244.1)     | 571.05 (243.4)             |
| Number of patients with dose reduction/total | 0/19           | 14/19          | 11/19              | 17/19                      |
| Mean reduction (SD), mg                      | 0              | 244.74 (201.3) | 203.13 (190.1)     | 334.21 (219.5)             |
| % of reduction vs initial dose               | 0              | 25.0           | 18.1               | 32.6                       |

Source: data collection sheet.

L-DOPA: levodopa; SD: standard deviation.

pallidotomy, whereas Fig. 5B shows the tracks made during subthalamotomy. More tracks were needed during subthalamotomy procedures, with a mean of 5.06.

It should be noted that multiple tracks were needed in both of the patients presenting intraparenchymal haemorrhages as a surgical complication (5 tracks in the pallidotomy procedure associated with this complication, and 6 in the subthalamotomy).

## Discussion

### Demographic characteristics of the sample

Currently, no absolute consensus has been established on when is the most appropriate time to perform surgical interventions in PD. Surgical treatment is indicated in patients at advanced stages of the disease, who present motor complications and loss of response to pharmacological treatment.<sup>11,54–56</sup> Numerous complications appear after 5 years of L-DOPA treatment that are difficult to control, despite the best possible dose adjustment.<sup>11,57–59</sup> At the time of the assessment prior to the first surgery, the mean age in our sample was 50 years, with a disease progression

time since diagnosis of approximately 9 years. Published series of patients undergoing surgical treatment show considerable diversity in patient age, with several reporting older ages at the time of surgical intervention.<sup>44,59,60</sup> However, the disease progression times reported at the time of surgery are very similar in the majority of studies, generally between 5 and 10 years.<sup>28,61,62</sup> Without a doubt, this is closely related to the fact that after 5 years of pharmacological treatment, complications begin to appear and the disease becomes more difficult to control.

PD is known to be more common among men.<sup>3,63,64</sup> However, our sample showed no significant difference in sex distribution, with a difference of 1 between the number of male and female patients; this is consistent with previous reports.<sup>26,65</sup> The left side was more frequently targeted in the first surgery, indicating that the right hemibody was more frequently affected.

### Dominant motor signs and complications in presurgical assessments

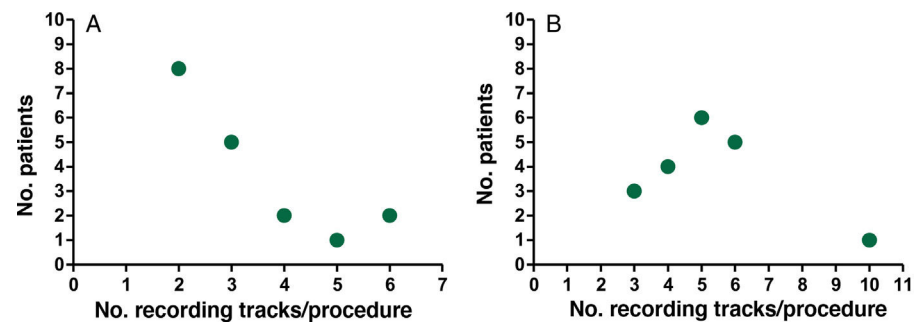
Although PD presents with unilateral onset and asymmetrical progression, its progressive nature means that both brain hemispheres (and consequently both sides of the body) are affected. In the light



**Table 6** Surgical complications.

| Complications           |     | Procedures (N = 38)    |                           |
|-------------------------|-----|------------------------|---------------------------|
|                         |     | Pallidotomies (n = 19) | Subthalamotomies (n = 19) |
| Unrelated to the lesion | IPH | 1                      | 1                         |
|                         | SWI | 1                      | 1                         |
| Related to the lesion   | SID | 0                      | 2                         |

Source: data collection sheet.  
IPH: intraparenchymal haemorrhage; SID: surgery-induced dyskinesia; SWI: surgical wound infection.



**Figure 5** Microelectrode recording tracks made in the functional surgeries. (A) Number of tracks made in pallidotomies,  $n = 19$ . (B) Number of tracks made in subthalamotomies,  $n = 19$ .

of this characteristic, surgical treatment generally requires a bilateral approach. This study presents the results of bilateral surgical treatment with an initial pallidotomy and a subsequent subthalamotomy.

All patients presented advanced, poorly controlled disease with motor complications. The GPi was targeted in the first procedure, given the high incidence of dyskinesia and dystonic postures observed in these patients. Some studies report improvements in dyskinesia after pallidotomy, and many study groups prefer to lesion this nucleus in this type of patients.<sup>11,65–68</sup> As the disease progresses, patients present motor deterioration, which is more evident in the hemibody contralateral to the surgical intervention. This is the basis for the indication of bilateral surgery, which is a common practice and depends on the progression of each patient. The patients in our study underwent subthalamotomy as the second procedure. Selection of the STN as a surgical target aims both to improve the patient's symptoms and to avoid the complications of bilateral pallidotomy.<sup>38,69,70</sup> The reported adverse effects of bilateral pallidotomy are severe, with speech and cognition being most severely affected; therefore, bilateral GPi ablation is not recommended in patients with PD.

### Motor behaviour

All patients included in the study presented dyskinesia or motor fluctuations at the time of the surgical intervention, despite receiving the best available pharmacological treatment. Disease severity, as measured by the Hoehn and Yahr scale,<sup>71</sup> was stage II in 5 patients and stage III in 14, indicating that all patients presented bilateral symptoms, axial involvement, and impaired postural reflexes. After both interventions, a significant improvement was observed in both motor performance and quality of life.

The main benefit of pallidotomy is the resolution of L-DOPA-induced contralateral dyskinesia, with ipsilateral dyskinesia also showing some improvement.<sup>60</sup> Previous studies have shown that GPi ablation largely improves bradykinesia and rigidity, with a smaller benefit for tremor. Our results showed that pallidotomy eliminated dyskinesia induced by dopaminergic medication in 100% of patients presenting this symptom, as well as the majority of other parkinsonian signs. Rigidity and bradykinesia were the signs showing the greatest change, although an improvement was also observed in tremor. Other groups have published similar results.<sup>27,60,72</sup>

The benefits of pallidotomy persisted for longer than a year, lasting up to 10 years in one patient. Nonetheless, disease progression led to an increase in disability both during OFF and ON states. This was clear in the results of the assessment performed prior to the second surgery (subthalamotomy), which showed an increase in MDS-UPDRS part III scores, although this increase was mostly due to involvement of the untreated hemibody and axial motor activity. Some authors report similar results in studies with follow-up periods of up to 5 years.<sup>55,61</sup>

After subthalamotomy, patients showed a greater improvement in parkinsonian signs and symptoms. We observed improvements in tremor, muscle tone, and bradykinesia, as well as gait, posture, postural stability, and speech. The motor outcomes observed in our series are consistent with other reports evaluating the short-term outcomes of ablative surgery.<sup>27,60,63,73–80</sup> According to Álvarez et al.,<sup>81</sup> rigidity and bradykinesia showed the greatest and longest-lasting response after subthalamotomy, whereas tremor displayed variable progression, over a follow-up period of 36 months.<sup>81</sup>

In our patients, the motor improvement after subthalamotomy was significantly greater than that observed after the first procedure. This is explained by the bilateral treatment effect achieved with the second intervention.

### Effects on daily levodopa dose

The clinical data reported in different studies show a significant reduction in medication use following subthalamotomy; this was not the case after pallidotomy.<sup>56,81</sup> However, dopaminergic medication doses were decreased within 6 months after pallidotomy in 70.6% of patients in our series. A literature search identified no similar reports in patients undergoing pallidotomy.<sup>56</sup> However, with the progression of the disease and the passage of time between procedures, with periods of up to 10 years in some cases, some patients' L-DOPA doses did gradually increase before the second surgery.

Unlike the results observed with pallidotomy, bilateral STN stimulation is reported to improve all the cardinal symptoms of PD, and medication doses can be reduced in over 50% of patients.<sup>56,82</sup> Tolosa et al.<sup>83</sup> report a reduction in medication of over 75%. Our results are consistent with these observations: it was possible to reduce L-DOPA doses in 88.2% of patients after subthalamotomy. Furthermore, the reduction in medication after subthalamotomy was even greater than that observed after pallidotomy. Although the impact of subthalamotomy on dopaminergic medication is well documented, the fact that this was the second procedure (completing the bihemispheric intervention) may have played a role in the reduction in patients' L-DOPA doses. We consider the results to demonstrate the good therapeutic effect of the combination of pallidotomy and subthalamotomy.

### Complications

Some authors report severe motor and psychiatric adverse effects in patients undergoing bilateral pallidotomy, including dysphagia, dysarthria, and cognitive alterations, among others.<sup>38,39,56,69</sup> Bilateral subthalamotomy has also been linked to less severe complications, including dyskinesia or hemichorea-ballism; speech disorders (hypophonia) and cognitive alterations have also been reported, although incidence is low.<sup>26,34,56</sup>

The combination of pallidotomy and subthalamotomy evaluated in this study represents a safe therapeutic alternative. Complications associated with the ablative lesion were minimal, with only 2 patients presenting mild dyskinesia induced by subthalamotomy. Furthermore, these abnormal movements resolved within one month of surgery in both cases. Neither patient developed moderate or severe dyskinesia. Among other causes, this may be related to transient dysfunction of a larger volume of the nucleus than the lesion area. Over the first 3 months after an ablative procedure, patients may present perilesional oedema associated with the radiofrequency lesion, influencing the functional effect of the lesion. Several authors have reported that this may be one explanation for the appearance of transient dyskinesia following procedures targeting the STN.<sup>25,84,85</sup>

Presence of dyskinesia induced by subthalamotomy is reported both in animal models of induced parkinsonism in monkeys, and in human patients; dyskinesia is characterised as unpredictable and cannot be explained by lesion volume alone.<sup>25,85</sup> The intranuclear location of the lesion is one possible explanation. In a retrospective analysis of patients undergoing surgery targeting the basal ganglia (thalamus or subthalamic region), it was observed that in cases in which dyskinesia was a significant manifestation, lesions were not exclusively intranuclear; postoperative MRI images showed that the STN lesion extended dorsally towards the anterior thalamus, ventrally towards the substantia nigra, and dorsocaudally through the zona incerta to the anterior limb of the internal capsule.<sup>28</sup> Several authors suggest that the presence of significant dyskinesia or ballismus after subthalamotomy is due to lesions greater than 20% of the volume of the lesion, or destruction of over 60% of the nuclear volume.<sup>34,44,86</sup>

However, the incidence of dyskinesia after subthalamotomy in our study was low. The selected lesion coordinates correspond

to the dorsolateral region of the nucleus, and include the zona incerta.<sup>44,45</sup> In the 2018 article "Subthalamotomy for Parkinson's disease: clinical outcome and topography of lesions," Rodríguez Rojas et al.<sup>44</sup> suggest that subthalamotomy is an effective option for the treatment of PD, but that the uncertainty regarding the optimal lesion location and the possibility of inducing hemichorea-ballism have restricted its use. The authors evaluated the correlation between the topography of radiofrequency lesions to the STN and motor improvement and the appearance of hemichorea-ballism. Patients were assessed before and after the procedure using the UPDRS motor score, MRI, and tractography. The study showed that lesions extending dorsally beyond the STN were less likely to cause hemichorea-ballism than those located entirely within the nucleus. Tractography findings showed that interruption of pallidothalamic fibres is probably associated with lower likelihood of postoperative hemichorea-ballism. The authors concluded that lesion topography is an important factor in the antiparkinsonian effect of subthalamotomy in patients with PD, and that lesions including the motor STN and pallidothalamic fibres induced a significant motor improvement and low incidence of hemichorea-ballism. Other authors report good results with stimulation of the zona incerta in patients with PD.<sup>87,88</sup>

Among the surgical complications unrelated to the ablative lesion, 2 patients developed intraparenchymal haemorrhages. Despite their small volume, the location of the bleeding in the area of the basal ganglia makes them a severe, life-threatening complication, rated as grade IV on the Clavien-Dindo classification.<sup>53</sup> Generally, the most severe complication of stereotactic surgery is cerebral haemorrhage<sup>21,44,53,86,89</sup>; although the incidence of symptomatic haemorrhage is generally below 2%, the reported rates greatly vary, ranging from 0% to 34%.<sup>60</sup> No consensus has been established on the relationship between number of microelectrode recording tracks and haemorrhage incidence. However, efforts are made to make the smallest possible number of tracks. Although the data indicate low incidence of haemorrhages, procedures involving 5 or more tracks seem to increase the likelihood of bleeding. This underscores the importance of proper preoperative planning to reduce the haemorrhage rate. Appropriate selection of the entry point, visualising the largest vessels and avoiding these and the lateral ventricles and cerebral sulci, are the main recommendations from the literature.<sup>45,90,91</sup>

An additional 2 patients developed infection of the surgical wound, requiring oral antibiotic treatment for 7 days. Studies in the literature report an infection rate of 1.2%–15.2%. This variation is largely explained by differences in the criteria used to define these infections.<sup>60</sup> Many factors are involved in postoperative wound infections: duration of the operation, number of professionals involved in the procedure, and even the patient's immunocompetence.

In our series, all patients recovered, with a 0% mortality rate. Morbidity was minimal. Of the patients presenting haemorrhage as a severe complication, one was asymptomatic, with a CT study at discharge showing resolution, and the other required a cycle of neurorehabilitation, achieving functional independence (90 points on the Karnofsky Performance Scale).<sup>92</sup>

Most of the adverse effects observed in our study were classified as being of moderate severity, partially interfering in patients' daily lives and requiring medical treatment. Only one case was classified as severe: the patient who presented symptomatic intracerebral haemorrhage, requiring specialist care in the intensive care unit for one week. All complications had a definitive cause.

A comparison of surgical complications after pallidotomy and after subthalamotomy revealed no significant differences. We believe that this is explained by the planning strategy employed by the surgical team for both procedures. The use of an automated surgical planning program that accounts for stereotactic atlas imagery and contrast CT images from the patient enables adjustment of approach angles and coordinates, avoiding large vessels and the lateral ventricles.<sup>45</sup>

These patients did not present complications related to speech or any other function, such as those reported in patients undergoing bilateral pallidotomy or subthalamotomy.<sup>12,26,39,93,94</sup>

## Conclusions

The combination of pallidotomy and subthalamotomy is an effective alternative for the treatment of complicated PD, enabling better motor control and a reduction in L-DOPA dose with a low rate of complications; furthermore, it avoids complications associated with bilateral pallidotomy and subthalamotomy, and is safe, even in patients with dyskinesia.

## Limitations and recommendations

Future research should include a prospective study with a homogeneous time between the 2 surgical procedures, with verification of the lesion volume and location, and an MRI tractography study; the lack of these aspects, mainly due to the retrospective approach of our study, constitutes its main limitation.

## Author contributions

Nelson Ernesto Quintanal Cordero (NEQC) presented the original idea; NEQC, Raisa Braña Miranda (RBM), Nancy Pavón Fuentes (NPF), and Ivonne Pedrosó Ibáñez (IPI) designed the study and analysed the results; NEQC and RBM drafted the article. NEQC, RBM, and IPI participated in pre- and post-operative patients assessments. All authors participated in the majority of the surgical procedures, in their respective areas of specialisation. All authors have read and approved the final version of the manuscript.

Throughout the process of research, drafting, review, and approval of the final document, the institutional affiliation of all authors was the International Center for Neurological Restoration (CIREN), in Havana, Cuba.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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