

Contribución Original

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Long-term neuropsychological effects in patients with Parkinson's disease who have undergone unilateral pallidotomy

Efectos neuropsicológicos a largo plazo en pacientes con enfermedad de Parkinson que han sido sometidos a palidotomía unilateral

Abstract

Introduction: Unilateral posteroventral pallidotomy (UPVP) has proven an effective treatment of motor symptoms in patients with advanced stages of Parkinson's disease (PD), however, the cognitive effects have not been clearly defined.

Objective: The aim of this study was to assess the clinical outcome of UPVP and its neuropsychological effects.

Methods: For this study we studied 10 subjects with advanced PD who underwent UPVP and 10 subjects with advanced PD who were candidates for surgery but did not undergo the surgery (control), with the follow administered tests mini-mental Parkinson (MMP), NEUROPSI, Beck depression inventory (BDI), beck anxiety inventory (BAI), and a statistical analyses with a Wilcoxon rank-sum test compared the pre-operative and 12-month values and their changes across patients and between groups.

Results: Neuropsychological testing revealed declines in visual detection but improvements on 20-minute delayed verbal recall at 12-month follow-up from UPVP.

Conclusions: Visual disorders could be related to affections of the pathway between the thalamus and posterior parietal cortical areas. The increase in delayed recall could be associated with an increased L-dopa effect from the basal ganglia to the prefrontal dorsolateral cortex related with UPVP.

Keywords

Globus pallidus, pallidotomy, Parkinson's disease, neuropsychology.

Resumen

Introducción: La palidotomía posteroventral unilateral (UPVP) ha resultado un efectivo tratamiento de los síntomas motores en pacientes en etapas avanzadas de la Enfermedad de Parkinson (EP), sin embargo los efectos cognitivos no han sido claramente definidos.

Objetivo: El objetivo de este estudio fue evaluar el efecto motor y neuropsicológico de la UPVP.

Métodos: Se incluyeron a diez sujetos con EP avanzada que se sometieron a UPVP y 10 sujetos con EP avanzada candidatos a UPVP, sin ser sometidos a ningún procedimiento quirúrgico (control), se evaluó el efecto motor y cognitivo, mediante la escala UPDRS III y con las pruebas: mini-mental Parkinson (MMP), NEUROPSI, inventario de depresión de Beck (BDI) y el inventario de ansiedad de Beck (BAI). Se realizó el análisis estadístico con una prueba de suma de rangos de Wilcoxon, mediante la que se compararon los valores preoperatorios y los cambios a los 12 meses entre los grupos.

Resultados: Se encontró que los pacientes sometidos a UPVP mostraron un decremento en las tareas de cancelación visual, sin estar dentro de los rangos de alteración, y se reconoció un incremento en recuperar en 20 minutos en la tarea de memoria verbal a los 12 meses de seguimiento de UPVP.

Conclusiones: El decremento en la tarea de cancelación visual podría estar relacionado con afecciones de la vía entre el tálamo y áreas corticales parietales posteriores. El aumento de la memoria diferida podría estar asociada con un aumento del efecto L-dopa a partir de los ganglios basales a la corteza prefrontal dorsolateral consecuencia de la UPVP.

Palabras clave

Enfermedad de Parkinson, globo pálido, neuropsicología, palidotomía.

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Introduction

For several decades, the unilateral lesion of the GPi has been shown to be a relatively safe and effective treatment for patients with Parkinson Disease (PD). Short-term follow-up studies have demonstrated that unilateral posteroventral pallidotomy (UPVP) improves all of the cardinal parkinsonian motor signs (tremor, rigidity, and bradykinesia) mainly on the contralateral side of the lesion, and also reduces dyskinesias.¹⁻⁴ In 2009 was shown the effects of unilateral pallidotomy in 18 patients with PD who were followed over the short term (3 to 8 months); these patients showed decreasing Unified Parkinson's Disease Rating Scale (UPDRS).⁵ Other studies have shown that pallidotomy improves PD symptoms for at least 3 years.⁶⁻⁸

Pallidotomy remains a valid procedure in many countries, being one of the most frequently used techniques. DBS have demonstrated better results than ablative procedures in advanced patients with PD.^{3,9} Surprisingly the 63.4% neurosurgical treatments were still using ablative methods, and the unilateral posteroventral is the mainly chosen in 52% of the cases, which explains the importance of clarifying the cognitive implications of this procedure.

In evaluating the effectiveness of pallidotomy, cognitive effects are as important as motor effects because the former may be even be more debilitating than motor symptoms.¹⁰ Additionally, it should be recognized that cognitive disorders are part of the natural course of PD, with consistent reports of deficits in processes of selective and sustained attention,^{11,12} reaction time,¹³ retrieval of the mnemonic trace,¹⁴ visuospatial abilities,¹⁵ naming failure¹² and articulation of language,¹⁶ as well as in executive function.¹⁷⁻²⁰ Moreover, it is estimated that approximately 80% of PD patients experience mood disorders at some point in their condition;²¹ between 40% and 60% exhibit depressive symptoms,¹⁸ and at least 40% exhibit anxiety symptoms. Despite the reliability of the benefits obtained by pallidotomy on motor symptoms,^{22,23} the cognitive implications are inconsistent.

Therefore, the objectives of this article are to describe the long-term neuropsychological effects of pallidotomy in a sample of bradykinetic PD patients before and after being subjected to unilateral GPi lesion and to compare these findings with control group patients not having undergone the surgery.

Methods

Patients from the outpatient clinic of the Department of Neurosurgery at the General Hospital of Mexico were included in the study. Those patients had idiopathic PD according to the criteria of the UK Brain Bank (National Collaborating Centre for Chronic Conditions. Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care.²⁴ These patients were resistant to treatment with L-dopa and did not have an associated neurological disease; they also had not received previous neurosurgical treatment and had no dementia according to the diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders.²⁵ This study was approved

by the ethics committee of our institution. Once the patients were informed of the diagnostic and surgical procedures, they were invited to participate in the research project and were requested to sign the informed consent form.

Two groups were formed: first, those patients who accepted the surgical procedure; second, those patients who, despite being eligible, did not accept surgery. The assessment of the clinical conditions of PD was performed using the Hoehn and Yahr scale and the UPDRS.²⁶

Neuropsychological Assessment

Patients were assessed before surgery and 12 months after surgery. Given that the consumption of L-dopa could influence the response, we decided to maintain the same dose three months prior to baseline and during the 12-month follow-up, if this regimen would not cause any complications for the patient.

The following neuropsychological assessment instruments were used:

1. Mini-Mental Parkinson (MMP).²⁷ In 2007, the Movement Disorder Society (MDS) proposed the Mini-Mental State Examination (MMSE) as an instrument for diagnosing and classifying dementia in PD. The MMP has been derived from the MMSE for the screening of cognitive impairment in PD by adding subtests that were focused on executive and visuospatial impairment. The MMP has been shown to have better psychometric properties than, greater screening capability than, and good convergent validity with the MMSE. This instrument assesses cognitive functions frequently affected in the course of PD (orientation, visual detection and memory, visual memory recall, alternating verbal fluency, set change and similarities). The application of the instrument takes approximately 10 minutes. Some of the advantages of MMP are its rapid administration and the potential to detect early cognitive changes in PD.
2. Abbreviated NEUROPSI.²⁸ This neuropsychological test allows the assessment of many cognitive functions (orientation, attention, memory, language, visuospatial processing and executive functions). It is individually administered, and its approximate duration is between 35 and 40 minutes for patients with cognitive disorders. It includes profiles according to age and education in the Mexican population. High sensitivity (91.6%) for identifying clinical pictures of dementia and high test-retest reliability (90.2%) have been reported, which are valuable in follow-up studies due to the lack of practice effects.

3. The Beck Anxiety Inventory (BAI) and the Beck Depression Inventory (BDI) with Mexican Adaptation.^{29,30} These instruments have been suggested by the American Academy of Neurology³⁰ for the neuropsychiatric examination of persons with PD and allow the assessment of symptoms of depression and anxiety.

Surgical Procedure

Under local anesthesia with 2% lidocaine, the Leibinger stereotactic frame (Inomed, Freiburg, Germany) was fixed to the skull, aligning it with the orbitomeatal line. Contrast helical computed tomography was performed. Axial slices were obtained to identify the plane between the anterior commissure (AC) and the posterior commissure (PC); the slices were 2 mm thick with no space between them and parallel to the AC-PC plane, and the coordinates were calculated with Praezis Plus V 3.0 software (Inomed, Germany) by an indirect method (X = 18 to 22 mm lateral, Y = 3.0 mm forward from the commissural midpoint, and Z = 3 to 4 mm below the anterior commissure-posterior commissure plane) and adjusted by a direct visualization method. Once the lesion site was determined, trephination was performed 5 mm anterior to the coronal suture, 30-35 mm lateral to the midline, in the anteroposterior direction 60-70° from the AP-PC line and 10-20° from the midsagittal plane in the mediolateral direction. The Riechert-Mundinger stereotactic frame (Inomed Freiburg, Germany) was used. Intraoperative clinical assessment was performed to observe adverse effects and the decrease in stiffness and bradykinesia contralateral to the operated site during bipolar stimulation at 100 Hz from 0.5 to 3.0 volts. Having identified these effects, a lesion of the selected brain area (GPI) was generated by radiofrequency thermocoagulation at 85°C for 90 seconds with a N50 device (Inomed Freiburg, Germany). Patients were discharged two to four days after surgery. Three months later, a brain MRI study was performed to verify the site and size of the lesion. Neuropsychological assessment was performed 12 months after surgery.

Statistical analyses were a Wilcoxon rank-sum test compared the pre-operative and 12-month values

and their changes across patients and between groups.

Results

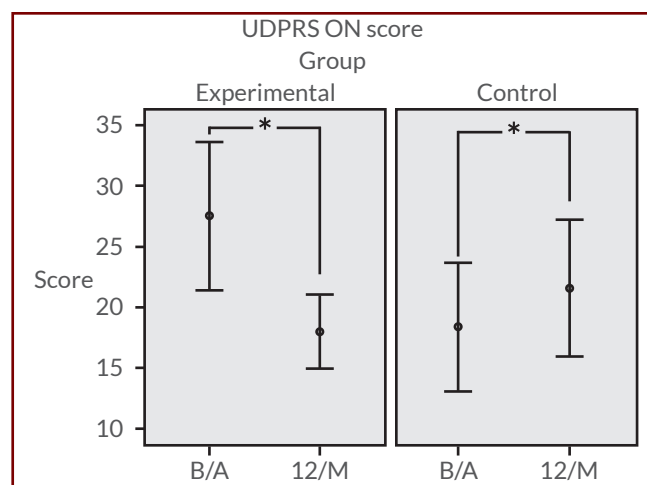


Figure 1. Graph showing the difference between the baseline assessment and the 12-month follow-up on the UPDRS ON (Chapter III). In the experimental group, there was a statistically significant decrease in the mean ($p = 0.01$), according to the Wilcoxon test. In the control group, there was a statistically significant increase in the mean ($p = 0.01$), according to the Wilcoxon test. Note: "B/A", Baseline Assessment, "12/M", 12-month-follow-up.

Twenty PD patients were included in the study. Ten male patients comprised the control group, whose mean age was 58.44 years (SD: ± 10.99), with 5.6 years of disease progression (SD: ± 1.42) and a mean L-dopa equivalent dose of 612.40 mg/day (SD: ± 306.21); their mean UPDRS III ON score was 27.5 (SD: ± 8.52), with 5 patients in stage III and 5 in stage IV, according to the Hoehn & Yahr scale. Ten patients comprised the experimental group—5 men and 5 women—whose mean age was 57.7 years (SD: ± 9.60) and whose conditions had progressed, on average, for 12.0 years (SD: ± 5.22). The experimental group's mean L-dopa equivalent dose was 903.87 mg/day (SD: ± 385.07); their mean UPDRS III ON score was 18.40 (SD: ± 7.39); and 6 patients were in stage III and 4 in stage IV, according to the Hoehn & Yahr scale. A difference was found

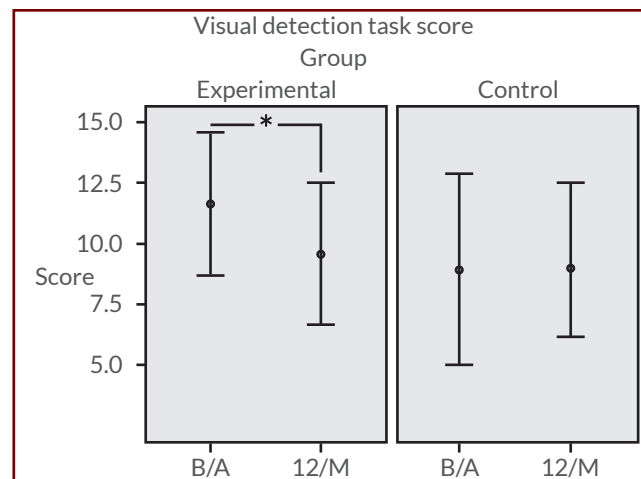


Figure 2. Graph showing the difference between the baseline assessment and the 12-month follow-up on the NEUROPSI Visual detection subtest scores. In the experimental group, there was a statistically significant decrease in the mean ($p = 0.01$), according to the Wilcoxon test, whereas in the control group, there were no statistically significant differences. Note: "B/A", Baseline Assessment, "12/M", 12-month-follow-up.

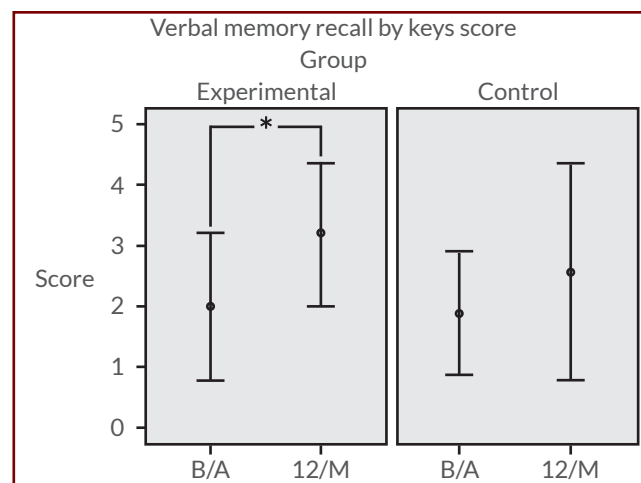


Figure 3. Graph showing the difference between the baseline assessment and the 12-month follow-up on the NEUROPSI Verbal memory recall by keys subtest scores. In the experimental group, there was a statistically significant increase in the mean ($p = 0.01$), according to the Wilcoxon test, whereas in the control group, there were no statistically significant differences. Note: "B/A", Baseline Assessment, "12/M", 12-month-follow-up.

for the UPDRS III ON score ($p = 0.01$), with the experimental group showing higher scores than the control group. Clinical conditions improved in patients in the experimental group, with an obvious significant increase in UPDRS after one year (*Figure 1*). Regarding neuropsychological performance, there was a statistically significant decrease in

the visual search task (when considering the performance of patients, according to the rules of the test, performance on the visual detection task was within normal range, even after one year) and a significant improvement in the verbal memory recall by keys task (*Figure 2 and 3*).

Discussion

To date, there is no consensus regarding long-term cognitive changes after pallidotomy, but it is possible to identify that the negative effects after six months of surgery appear to be transient ones, given that they do not show significant differences at 12 months compared to the initial values.

Cognitive sequelae although neuropsychological reports are inconsistent defined due to the methodological characteristics of past studies, including the criteria for sample selection, short follow-up periods (3 or 6 months after pallidotomy), and lack of verification of the lesion.

This article provides a description of the long-term neuropsychological effects experienced by patients with refractory PD undergoing GPi lesioning. Using the data obtained in this study, we can state that clinical conditions improved in patients in the experimental group, with an evident increase in UPDRS after one year; moreover, despite there being a statistically significant decrease in the Visual Cancellation task, the clinical conditions remained within normal ranges. However, a statistically significant improvement was identified in the verbal memory recall by keys task, suggesting that there is a benefit in dopaminergic projections to the dorsolateral prefrontal cortex after pallidotomy.

Mental Status

Findings based on the application of mental status scales, as reported by some authors,^{32,33} may be explained by years of disease progression (up to 20 years) or by postoperative complications.³² However, the lack of post-operative effects on

screening tests are not completely method to recognize cognitive functioning and requires more extensive neuropsychological batteries with greater specificity in the assessment of significant processes are required. Furthermore, these scales are affected by characteristics such as the age, schooling and culture of the patients assessed;³⁴ thus, it is really important to consider batteries that include normative data by age and educational level, such as the NEUROPSI battery to Mexican population.

Attention

Attention effects after pallidotomy have been verified using different types of tests; some authors cite an increase in performance within 6 months of the surgery,³² but these data were not replicated by Uitti³⁵ other data indicate no cognitive effect associated with the lesion for up to 1 year after surgery.^{35,36} In contrast, Trepanier⁴ reported decreases in the execution of attention tasks in 4% of patients at 6 months; however, their execution showed no statistically significant differences 12 months after surgery. We found a decrease in the Visual Cancellation task, which is related to processes of selective attention; we found a statistically significant decrease in execution in patients undergoing GPi lesioning but not in the control group. Comparing these findings with standardized scores, we found that these remained within normal ranges despite the statistically significant differences, so we did not consider pallidotomy to be clinically detrimental to the patients who underwent the operation.

Memory

According to the findings of previous studies, the total scores of patients on auditory verbal memory tasks do not statistically changes after 6 months,^{5,33,36,37,38} 1 year,^{32,35,36-38} or 4 years.⁵ From our findings, changes in scores of the memory curve at the 12-month follow-up were identified in neither the control nor the experimental group, which coincides with previous findings.^{32,35-38} Previous findings on visuospatial memory tasks have shown no changes at 6 or 12 months;^{4,38} this absence of change was replicated in our findings. When scores on memory recall are considered, declines have been identified at 6 months^{4,32} but there is little consistency when measuring the long-term effect (> 12 months); Baron³² suggested that these scores increase, whereas Trepanier⁴ reported that patients return to their initial performance. The results of our study support those of Baron.³²

Language

On naming and vocabulary tasks, no effects have been associated with GPi lesions after 6 and 12 months.^{32,33,35,37,38} In the previous literature, inconsistent data have been found regarding both semantic and phonological verbal fluency tasks, with some authors reporting a significant decrease at 6 months^{4,35,37,38} that progresses by 12 months,^{4,35} (whereas others have not noted an effect on these tasks after 6 or 12 months.³⁷ We consider the possibility that the effects at 6 months might be transient; at our 12-month follow-up, no statistically significant changes were identified.^{32,33,36,38}

Motor

Few studies have included the execution of motor tasks; some have described an increase within 6 months following surgery.³⁵ At 12 months, there were no significant differences from baseline, but other studies have found no changes in performing tasks such as tapping and pegboard at 12-month follow-ups;^{32,37} we did not identify those changes either.

Visuospatial processing

Affected execution of visuospatial processing tasks, such as cube design, copying figures, and

line orientation, has been described in PD patients; regarding the effects of ablation of the GPi, Alegret³⁶ reported an increase in the execution of the line orientation task at a 6-month follow-up and a return to baseline after 4 years. However, in the cube design and copying figures tasks, there were no differences after 6 or 12 months or even after 5 years.⁵ For a semicomplex figure copy task, after 12 months, we did not find changes associated with the GPi lesion; these results corroborate those reported.^{4,5,35,38}

Executive Functions

Findings regarding the postoperative effects associated with pallidotomy are limited because few tasks have been evaluated in previous studies.^{4,5,32,36,35,37} For the execution of the digit span backward task, findings have been contradictory, at least during the first 6 months; Baron³² found an improvement in execution, whereas Trépanier⁴ found a decline in execution. Findings at a 12-month follow-up suggest that execution returns to baseline ranges,^{4,32} and no significant differences were identified at a 5-year follow-up.³⁷ Regarding pallidotomy patients' execution of mental flexibility tasks, such as the Wisconsin Card Sorting Test (WCST), findings seem to be consistent, showing no effects at either 6 or 12 months,^{5,35,36,38} even at a 5-year follow-up.⁵ We found no statistically significant changes in either the control group or the experimental group on executive functions tasks.

Mood

Regarding levels of anxiety and depression, no previous studies have identified changes associated with the GPi lesion at either 6 months, 12 months.^{5,32,35,36,37} Our data replicate previous results insofar as we did not identify changes on inventories for anxiety or depression at the 12-month follow-ups for either group.

Conclusions

Previous neuropsychological reports are inconsistent biases in these studies are due to poor sample selection criteria, short follow-up periods (3 or 6 months after pallidotomy), and the lack of verification of lesion location.^{23,39,40,41,42,43} Consistent with previous research studies, UPVP produced significant benefits in motor symptoms (mainly, bradykinesia). The follow up after UPVP have to consider cognitive and psychiatric effect, additionally stereotactic surgery for movement disorders needs an interdisciplinary approach in order to select patients appropriately.²¹ Contrary

to reports of declines in cognitive functions, we did not find significant declines associated with surgery. UPVP remains a safe and effective surgery for advanced PD patients, less expensive technique than DBS option. The UPVP may be a reasonable strategy for emerging countries to overcome barriers in the treatment of Parkinson²¹ but requires a multidisciplinary approach includes neuropsychologist assessment, extensive selection criteria, large follow-up periods and the lack of verification of lesion location.

Relevant conflicts of interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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