

Deep brain stimulation in parkinson disease

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.

The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

INTRODUCTION

Deep brain stimulation is a form of neuromodulation and consists of the surgical implantation of electrodes used to directly stimulate specific regions of the brain according to the pathology.

The precise anatomical localization of these regions is made by stereotactic mapping, combining images obtained from magnetic resonance imaging and computed tomography in addition to the intraoperative physiological mapping used to refine the implant targets.

During the placement of the electrodes, the activity of neurons that demarcate deep functional regions of the brain is recorded using microelectrodes followed by electrical stimuli that allow to test the acute effect of the stimulation and adjust its intensity and the placement of the electrodes.

The effective deep brain stimulation (DBS) in the subthalamic nucleus (STN) imposes a new pattern of activity within the brain circuits, favoring the alpha and gamma neuronal discharge and restoring the thalamocortical transmission through the axonal activation. In patients submitted to the early protocol, the change in the endogenous transmitters and the recovery of plasticity are competing factors. In advanced stages, the remodulation of endogenous band

frequencies, the rupture of the pathological pattern and/or antidromic cortical activation are probably the prominent modes.

The conventional deep brain stimulation (cDBS) of the subthalamic nucleus (STN) or the internal globus pallidus (GPi) is an established treatment for advanced stage Parkinson Disease (PD). Although cDBS improves motor symptoms of PD in the short and long term, it has limitations, such as the induction side effects, such as dysarthria, imbalance, and dyskinesia, and can also require regular adjustments in the stimulation, especially in the first phase after surgery. In addition, cDBS has limited battery life.

METHODOLOGY

With the objective of identifying the best evidence available, at the present time, related to the use of deep brain stimulation in patients with Parkinson disease, we developed a systematic review of the literature using the Medline/PubMed database and the following search strategy: (Parkinson) AND (Surgery OR Deep Brain Stimulation OR Electric Stimulation Therapy OR Electrical Stimulation) AND random*.

We included studies with randomized controlled clinical trial design, which were assessed based on randomization, blinded allocation, double-blind, losses < 20%, prognostic characteristics, outcomes (adequate, time, measurement), analysis per intention to treat, sample size calculation, others, and JADAD score).

The results regarding the clinical situation considered (Parkinson disease) were exposed individually, using the following items: number of studies selected (according to the inclusion criteria), main reasons for exclusion, a description of the results and synthesis of the evidence available; for results with evidence available, the following were specifically defined whenever possible: the population, the intervention, the outcomes, the presence or absence of benefit and/or harm, and the controversies; studies on issues related to cost were not included. The outcomes considered were limited to the effectiveness and safety of interventions. The results were presented preferably in absolute data, absolute risk, number needed to treat (NNT), or number needed to harm (NNH) and, eventually, in mean and standard deviation values.

We retrieved 435 papers, and after evaluating their title, abstract and full text, only 9 jobs were selected to support the synthesis of the evidence available (Figure 1).

RESULTS

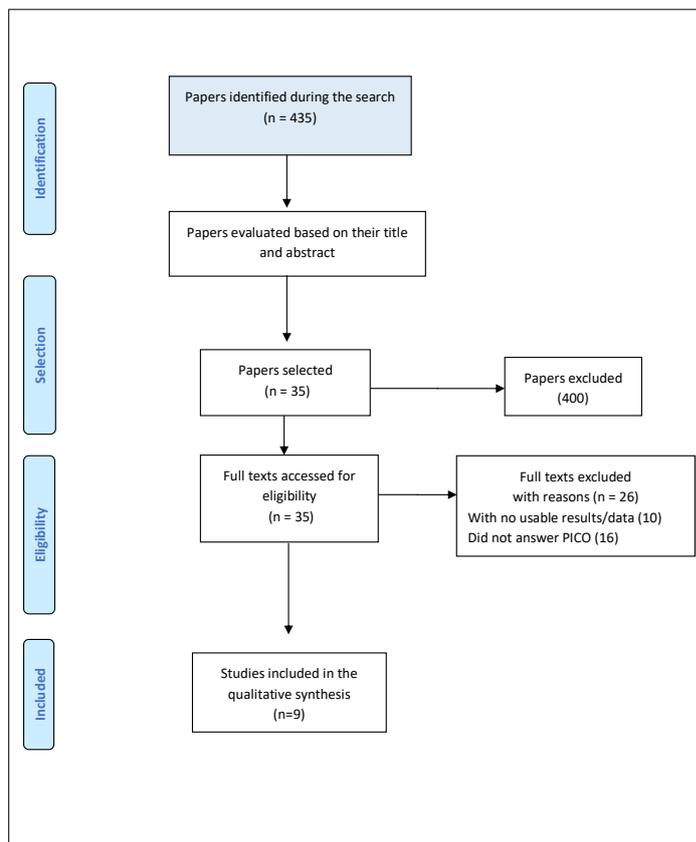
In patients with idiopathic PD for at least 5 years; younger than 75 years; with limitation of daily activities due to motor problems or dyskinesia, in spite of the clinical treatment; without dementia (total MDRS score > 130) or any severe psychiatric disease; without surgical contraindication; bilateral DBS of the STN compared with optimized clinical treatment, analysis of 6 months of DBS¹⁻⁴:

- Improvement of the quality of life (Table of contents of the PQD-39 [0-100]), compared to the period prior to the implant (baseline), on average, by 9.5 (-9.5) points in DBS group and worsening by 0.2 (+0.2) points in the group with optimized clinical treatment alone; $p = 0.001$. The domains with statistical significance were mobility, daily living activities, and body discomfort. There was no difference in cognition; ($p = 0.44$).
- There is no difference when compared with

patients with scores in the lowest quartile of MDRS (130 - 137 points) on quality of life; $p > 0.05$.

- There was improvement in Part II of the UPDRS (daily living activities) both in the ON state (ON stimulation/ON medication) as in the OFF state (ON stimulation/OFF medication) ($p < 0,005$) for both comparisons between the groups; the same results were observed for Part II of the PDRS (motor function).
- Dyskinesia (Dyskinesia Scale) was improved with the use of medication ($p < 0.001$); however, not without it ($p = 0.78$).
- It reduced the daily use of levodopa or equivalent dose of another medication; ($p < 0.001$).
- It did not decrease or increase dementia (Mattis Dementia Rating Scale) or depression (Montgomery and Asberg Depression Rating Scale); $p > 0.05$.
- It improved the quality of life both physical and mental (SF-36); $p < 0.05$.

FIGURE 1. THE SELECTION OF RETRIEVED FROM THE VIRTUAL DATABASES OF SCIENTIFIC INFORMATION IS DETAILED IN THE FLOWCHART BELOW



- It increased the risk of severe adverse events in 9% (death from any cause, suicide, hospital re-admission with worsening of mobility or infection); (NNH = 11).

In 13% of patients submitted to DBS, there were severe adverse events (intracerebral hemorrhage with death, suicide, infection at the site of the device)¹⁻⁴.

In patients younger than 55 years; Parkinson disease with an evolution time of 5 to 10 years; motor symptoms of mild to moderate intensity (Hoehn and Yahr stage ≤ 3); fluctuations of motor response with "OFF" period for more than 25% of the of the day; with any professional activity; normal brain magnetic resonance; absence of severe psychiatric diseases; absence of dementia (Mattis Dementia Rating Scale score $> 130/144$); impairment of social and occupational function due to PD (Social and Occupational Functioning Assessment Scale [SOFAS] score between 51 and 80%), bilateral DBS in the STN, compared with optimized clinical treatment, in the 18-months analysis⁵:

- Improvement of the quality of life (Table of contents of the PQD-39 [0-100]), compared to the period prior to the implant (baseline), on average, by 6.5 (-6.5) points in DBS group and worsening by 4.0 (+4.0) points in the group with optimized clinical treatment alone; $p = 0.001$.
- It improved activities of daily living (UPDR Part II, OFF medication); MD = 8.8; [95% CI 3.15 to 14.44]; $p = 0.004$.
- There was no difference in daily living activities (UPDR Part II, ON medication); MD = 1.2; [95% CI -1.08 to 3.48]; $p = 0.28$.
- It improved motor function when there was no use of levodopa (UPDR Part III); $p < 0.05$.
- It decreased motor complications (dyskinesia, motor fluctuation) induced by levodopa (UPDR Part IV); $p < 0.05$.
- It reduced the daily dose of levodopa or equivalent; $p < 0.001$.
- There was no difference in cognition (Mattis Dementia Rating Scale [MDR]); $p > 0.05$.
- There was no difference in the psychiatric evaluation using the following scales: Mattis Dementia Rating Scale; Comprehensive Psychiatric Rating Scale; Montgomery-Asberg Depression Rating Scale; BriefAnxiety Scale; $p > 0.05$.
- There was no difference in the number of adverse events; $p > 0.05$.

No severe adverse effects were observed associated with the procedure⁵.

In patients with an average age of 62 years; idiopathic Parkinson's disease diagnosed 12 years ago (average); Hoehn and Yahr stage greater than or equal to 2 when there is no use of medication; responsive to levodopa; with persistent incapacitating symptoms (motor fluctuation, dyskinesia), in spite of the medication; with poor motor function or control of symptoms for at least 3 hours over a period of 24 hours; receiving stable medical treatment for at least 1 month; no abuse of alcohol or drugs; without dementia or pregnancy; bilateral DBS of the STN (n=60) or of the GPi (n=61) compared with optimized clinical treatment, at the 6-months assessment of DBS⁶:

- It increased the time of the ON state on average by 4.5 h/day (without troublesome dyskinesia). MD 4.5 h/d (95% CI 3.7 to 5.4 h/d); [$p < 0.001$].
- It decreased the time of the OFF state on average by 2.5 h/day ($p < 0.001$).
- It improved motor function when there was no use of medication (UPDR Part III); MD = 10.6 (95% CI 8.1 a 13.2), $p < 0.001$.
- It improved daily living activities (UPDR Part II); MD = 4.6 (95% CI 3.4 to 5.9), $p < 0.001$.
- It decreased complications from the therapy (UPDR Part IV); MD = 2.9 (95% CI 2.1 to 3.7), $p < 0.001$.
- It improved the quality of life (PDQ-39) in the domains of mobility, daily living activities, cognition, body discomfort, and communication. ($p < 0.01$).
- It increased the risk of at least one serious adverse event (fall, dystonia, confusional state) in 29% (NNH = 3).

In 29% of patients submitted to DBS, there was at least one severe adverse event: cerebral hemorrhage, infection related to the surgical procedure or the device⁶.

In patients with advanced Parkinson Disease (PD) with at least 5 years of evolution; a mean age of 59 years; without adequate control with drug therapy; without cognitive problems or significant psychiatric conditions; the use of DBS in the STN (174) or GPi (4) combined with optimized clinical treatment compared with optimized clinical treatment, in the 1-year analysis⁷:

- Improvement of the quality of life (Table of contents of the PQD-39 [0-100]), compared to the period prior to the implant (baseline), on aver-

age, by 5.0 (-5.0) points in DBS group and by 0.3 (-0.3) points in the group with optimized clinical treatment alone; (MD = -4.7 [95% CI -7.6 to -1.8]; $p = 0.001$). The domains with statistical significance were mobility, daily living activities, and body discomfort. There was no difference in the domain of cognition ($p = 0.17$).

- There was improvement in Part II of the UPDRS (daily living activities) both in the ON state (ON stimulation/ON medication) as in the OFF state (ON stimulation/OFF medication) ($p < 0.0001$) for both comparisons between the groups; the same results were observed for Part III of the PDRS (motor function).
- There was no difference, up to one year, in the assessment of cognitive function (DRS-II); MD = 0.05; 95% CI 9.4 to 0.8.
- It increased the risk of adverse events related to surgery in 20% (NNH = 5); analysis per intention to treat.
- There was no difference in severe adverse events related to PD or drug therapy; NNH = NS.

In the surgery group (DBS), 19% presented severe adverse events related to the surgery (hemorrhage, infection)⁷.

In patients 52 years old (on average); Parkinson disease with an evolution time of 7.5 years (average); motor symptoms of mild to moderate intensity in the "ON" state of medication (Hoehn and Yahr stage < 3); improvement of 50% or more of the motor signals with dopaminergic drugs, assessed with the Unified Parkinson's Disease Rating Scale, Part III (UPDRS-III [0 - 108]); fluctuations of motor response and dyskinesia present for 3 years or less; score greater than 6 (UPDRS-II) for daily living activities, at the worst condition, in spite of medical treatment; impairment in social and occupational function due to PD (Social and occupational Functioning Assessment Scale [SO-FAS] score between 51 and 80%); absence of dementia (Mattis Dementia Rating Scale score > 130 [0 to 144]); absence of depression with suicidal thoughts with a score lower than 25 in the Beck Depression Inventory II (0 to 63); absence of severe psychiatric disease, bilateral DBS in the STN compared with optimized clinical treatment, in the 24-months analysis⁸:

- It improved the quality of life (Table of contents of the PQD-39 [0-100]);
- MD = 8.0±1.6 (95% CI = 4.2 to 11.9; $p = 0.002$).
- It improved motor function when there was no

use of medication (UPDR Part III); MD = 16.4±1.4 95% CI = 13.7 to 19.1); $p < 0.001$.

- It improved daily living activities during the worst conditions (UPDR Part II); MD = 6.2±0.9 (95% CI = 4.5 to 8.0); $p < 0.001$.
- It decreased motor complications induced by levodopa (UPDR Part IV); MD = 4.1±0.4 (95% CI = 3.2 to 4.9); $p < 0.001$.
- It increased the time (hs) with good mobility and without dyskinesia; MD=1.9±0.8 (95% CI = 0.4 to 3.4); $p = 0.01$.
- It reduced the daily dose (mg) of levodopa or equivalent; $p < 0.001$.
- There was no difference in cognition (Mattis Dementia Rating Scale [MDR]); $p = 0.28$.
- There was no difference in the cognitive assessments using the Mattis Dementia Rating Scale or UPDRS-I; $p > 0.05$.
- It improved mood, assessed by the examiner (Montgomery and Asberg Depression Rating Scale) and by the patient (Beck Depression Inventory II); $p < 0.05$.
- It improved the general psychiatric morbidity (Brief Psychiatric Rating Scale); $p < 0.05$.
- There was no difference in the evaluation of apathy (Starkstein Apathy Scale); $p = 0.08$.
- There was no difference in risk of severe adverse events (death by suicide, an event that threatens the life, marked worsening of symptoms of PD, psychosis, suicidal ideation); (NNH = NS).

Severe adverse events related to surgery (cerebral abscess, nonspecific edema) or to the device (displacement, re-operation), occurred in 17.7% of the patients⁸.

Patients with idiopathic Parkinson's disease stage 2 or higher (Hoehn and Yahr scale) with persistent and disabling symptoms despite optimal medical therapy were submitted to optimized drug therapy (N: 134) or to the surgical implantation of a bilateral deep brain stimulator (N: 182) at the lower subthalamic regions or the internal globus pallidus. The outcomes considered were neuropsychological and related to the Parkinson's Disease Questionnaire (PDQ - 39)⁹.

The subthalamic stimulation was associated with a higher average of reductions in some measurements of processing speed of ideas; the globus pallidus was associated to a lower average of performance on a measurement of learning and memory

FIGURE 2. RISK OF BIAS IN RANDOMIZED CLINICAL TRIALS - EVALUATION OF DEEP BRAIN STIMULATION IN PARKINSON'S DISEASE

| DESCRIPTIVE TABLE OF THE BIASES OF THE RANDOMIZED CLINICAL TRIALS INCLUDED | | | | | | | | | | |
|--|----------------|------------------------|--------------------|-----------------|---------------|---|----------|-----------------------------|-------------------------|-------|
| Study | Question Focus | Randomization Adequate | Allocation Blinded | Double Blinding | Losses (<20%) | Characteristics Prognostic or demographic | Outcomes | Intention-to-treat analysis | Sample size calculation | Jadad |
| Deuschl G 2006 | | | | | | | | | | 3 |
| Witt K 2008 | | | | | | | | | | 3 |
| Daniels C 2011 | | | | | | | | | | 3 |
| Witt K 2011 | | | | | | | | | | 3 |
| Schüpbach WM 2007 | | | | | | | | | | 2 |
| Weaver FM 2009 | | | | | | | | | | 3 |
| Williams A 2010 | | | | | | | | | | 3 |
| Schuepbach WM 2013 | | | | | | | | | | 3 |
| Rothlind JC 2015 | | | | | | | | | | 2 |

■ : absence of bias
■ : presence of bias
■ : no information

that requires mental control and cognitive flexibility. In comparison with the group who received medication, the intervention group had, at the 6-months follow-up, a significantly higher average of reduction in several measurements for the performance of the processing speed and memory, as well as on the test for neuropsychological performance. There was a significant reduction by 8% in favor of the medication in the decline in two or more cognitive domains, which had a negative effect in the assessments of daily functioning and quality of life (QOL)⁹.

RECOMMENDATION

Benefits

In patients with idiopathic PD; evolution time greater than 5 years; without incapacitating cognitive or psychiatric problems; without adequate control with drug therapy, but responsive to levodopa in

an acute test conducted by a specialized neurologist, *the DBS of the STN or GPi compared with the optimized clinical treatment* for a period of up to 24 months: improves the quality of life and the motor function. The daily dose of L-dopa is reduced significantly only with implants in the subthalamic nucleus.

Harm

It increases the risk of severe adverse events (death from any cause, suicide, hospital readmission with worsening of mobility or infection, fall, dystonia, confusional state), at an index that can vary from 9 to 29%;(NNH = 3 - 11).

The occurrence of at least one *severe adverse effect related to the surgery or device* (DBS group) ranges from 13 to 29% (median of 17%).

There is no benefit or harm

In cognition and in the psychiatric evaluation.

REFERENCES

1. Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, et al; German Parkinson Study Group, Neurostimulation Section. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006 31;355(9):896-908. PMID: 16943402.
2. Witt K, Daniels C, Reiff J, Krack P, Volkmann J, Pinsker MO, et al. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. *Lancet Neurol* 2008;7(7):605-14. PMID: 18538636.
3. Daniels C, Krack P, Volkmann J, Raethjen J, Pinsker MO, Kloss M, et al. Is improvement in the quality of life after subthalamic nucleus stimulation in Parkinson's disease predictable? *Mov Disord* 2011;26(14):2516-21. PMID: 22170276.
4. Witt K, Daniels C, Krack P, Volkmann J, Pinsker MO, Kloss M, et al. Negative impact of borderline global cognitive scores on quality of life after subthalamic nucleus stimulation in Parkinson's disease. *J Neurol Sci* 2011;310(1-2):261-6. PMID: 21733529.
5. Schüpbach WM, Maltête D, Houeto JL, du Montcel ST, Mallet L, Welter ML, et al. Neurosurgery at an earlier stage of Parkinson disease: a randomized, controlled trial. *Neurology* 2007 23;68(4):267-71. PMID: 17151341.
6. Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks WJ Jr, et al; CSP 468 Study Group. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 2009 7;301(1):63-73. PMID: 19126811.
7. Williams A, Gill S, Varma T, Jenkinson C, Quinn N, Mitchell R, et al; PD SURG Collaborative Group. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol* 2010;9(6):581-91. PMID: 20434403.
8. Schuepbach WM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, Hälbig TD et al; EARLYSTIM Study Group. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med* 2013 14;368(7):610-22. doi: 10.1056/NEJMoa1205158. PMID: 23406026.
9. Rothlind JC, York MK, Carlson K, Luo P, Marks WJ Jr, Weaver FM, et al. Neuropsychological changes following deep brain stimulation surgery for Parkinson's disease: comparisons of treatment at pallidal and subthalamic targets versus best medical therapy. *J Neurol Neurosurg Psychiatry* 2015; 86: 622-9. doi: 10.1136/jnnp-2014-308119. PMID: 25185211.

