Deep Brain Stimulation in Patients with Parkinson’s Disease: Effect on Psychiatric Symptoms and Quality of Life

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- deep brain stimulation

Abstract

Background and Study Aims To determine the effect on psychiatric symptoms and quality of life in 30 patients with Parkinson’s disease (PD) treated with deep brain stimulation (DBS) of both subthalamic nuclei (STN) after 1 year of follow-up.

Material and Method We conducted a prospective 1-year follow-up study with a baseline assessment before and 6 and 12 months after surgery. The following were used as assessment instruments: the Bech-Rafaelsen Melancholia Scale (MES), the Bech-Rafaelsen Mania Scale (MAS), the Beck Scale for Suicidal Ideation (SSI), the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), the Oviedo Sleep Questionnaire (OSQ), the 36-Item Short Form Health Survey (SF-36), the Unified Parkinson’s Disease Rating Scale (UPDRS), the dose of levodopa, and the active contact stereotactic coordinates.

Results We recorded a clinical improvement between baseline with medication use (ON medication) and the results obtained at 6 and 12 months with medication use and stimulation (ON stimulation, ON medication) in MES and OSQ (p < 0.0001) and in SF-36 (p < 0.005). No changes were observed in MAS and SSI. There was a clinical improvement between baseline with ON medication and the results obtained at 12 months with ON stimulation, ON medication in Y-BOCS (p < 0.04). Also, there was a 53.3% reduction in levodopa at 6 months and a 54.7% reduction at 12 months after surgery (p < 0.0001). There was an improvement between baseline with OFF medication and the results obtained at 6 and 12 months OFF medication, ON stimulation (p < 0.0001) in UPDRS-III. There were no statistically significant differences between the initial and final active contact coordinates, or between stimulation parameters.

Conclusions DBS of the STN in patients with PD is associated with an improvement in psychiatric (affective and sleep-wake cycle) symptoms, clinical motor symptoms, and quality of life at 1 year after surgery.

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Introduction

Parkinson’s disease (PD) is an idiopathic degenerative, irreversible disorder of the extrapyramidal system, due to a deficit of dopamine in the nigrostriatal system, characterized by resting tremor, rigidity, bradykinesia, and postural instability. It has a prevalence of 120 to 160/100,000 population and an incidence of 16/100,000 population/year. Genetic forms of PD have been identified. The so-called nonmotor symptoms (NMS) of PD are common in these patients, with the most relevant ones associated with the autonomic nervous system and psychiatric symptoms. Some authors claim that psychiatric symptoms are so common in patients with PD that they should be considered an integral part of the disease. The most common symptoms in PD according to their prevalence include depression, anxiety, apathy, and psychosis.

Deep brain stimulation (DBS) of the dorsolateral part of the subthalamic nucleus (STN) is one of the accepted treatments for patients with advanced PD resistant to medication, rated as evidence level A. Stimulation may be beneficial at an earlier stage of PD. There are other options such as chronic parenteral apomorphine or levodopa-carbidopa intestinal administration.

High-frequency DBS leads to a kind of functional deafferentation of the stimulated structure and to the modulation of cortical activity (both ortho- and antidromically). Which effects are relevant to the therapeutic effects of DBS is still unclear.

Bearing in mind that STN DBS may cause psychiatric complications in patients with PD, our aim was to determine the effect on psychiatric symptoms and quality of life in patients with PD treated with DBS of the STN after 1 year of follow-up.

Material and Methods

A naturalistic observational, prospective 1-year follow-up study with three assessments, one baseline or screening assessment before surgery, one at 6 months after surgery, and finally one at 12 months after surgery. The sample size was 30 patients undergoing surgery over 2 years. All patients included in the study were operated on in the same center, by the same surgical team, and using the same methodology. With the aim to define the STN somatosensory region as precisely as possible, the target point was obtained after a minimum number of three neurophysiologic microelectrode recordings. Control computed tomography (CT) was performed on every patient directly after the surgical procedure, with the stereotactic frame in place, to check the coordinates of the implanted DBS leads with respect to the mid-intercommissural point (ICP).

The stimulation parameters were adjusted, until clinical optimization was achieved with an upper diminution to 30% in the Unified Parkinson’s Disease Rating Scale (part 3). The lead contact most frequently used was the third, corresponding with STN in the dorsal border. In theory, this contact affects both the neurons and the STN axons.

All of the patients agreed to participate in the study. The assessments were conducted by a single interviewer in all cases. Interviews with spouses, family, and caregivers were important sources of information. The study was approved by the local ethics committee.

The following were used as assessment instruments: information on sociodemographic variables (age, sex, marital status, educational level, work activity) and clinical variables (time since onset of PD, drug treatment for PD, history and/or current presence of mental and/or behavioral disorder, history, and/or current use of psychopharmacological/psychotherapeutic treatment), the Bech-Rafaelsen Melancholia Scale (MES), the Bech-Rafaelsen Mania Scale (MAS), the Beck Scale for Suicidal Ideation (SSI), the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), the Oviedo Sleep Questionnaire (OSQ), the 36-Item Short Form Health Survey (SF-36), the Unified Parkinson’s Disease Rating Scale (UPDRS-III), the dose of levodopa, and the active contact stereotactic coordinates.

The specific objectives were (1) to identify changes in affective (depressive and manic) symptoms using the MES and MAS scales after DBS of the STN, (2) to identify changes in suicidal ideation using the SSI scale after DBS of the STN, (3) to identify changes in obsessive-compulsive symptoms using the Y-BOCS scale after DBS of the STN, (4) to identify changes in sleep-wake cycle symptoms using the OSQ scale after DBS of the STN, (5) to determine changes in quality of life using the SF-36 scale after DBS of the STN, (6) to determine motor improvement using the UPDRS-III scale and reduction in levodopa, and (7) to determine the location of the active contact with respect to the dorsolateral region of the STN.

For the statistical processing of the data, SPSS software v.17.0 (IBM, Inc., Armonk, New York, United States) was used. In all cases, a p value < 0.05 was considered significant. For descriptive statistics, in the case of quantitative variables, the mean and standard deviation (SD) were used. For descriptive statistics, in the case of qualitative variables, frequency and percentage were used. The determination of the relationship between different variables was made using the chi-square test in the case of two qualitative variables and the Student t test in the case of one qualitative variable and one quantitative variable with two categories. To determine time-based differences in clinical parameters, the Student t test for paired samples was used. Finally, to determine the active contact (activated contact) coordinates, the method just described was used.

Results

The sample consisted of 30 patients, 20 male and 10 female, with a mean age of 58.7 years, of whom 14 patients (46.7%) were receiving psychiatric treatment and 18 patients (60%) were receiving medical treatment for somatic diseases. The mean time since onset of PD was 11.2 years ± 3.6 SDs.

MES

A reduction was observed in mean score, with p < 0.0001, between baseline ON medication and the assessment conducted at 6 months (ON medication-ON stimulation: DBS of the STN) of 7.4 points (13.3 ± 5.2 SDs to 5.9 ± 4.0 SDs) and at
12 months (ON medication-ON stimulation) of 8 points (13.3 ± 5.2 SDs to 5 ± 3.9 SDs). This correlated with a clinical improvement in the patients. Otherwise, no statistically significant differences were found between the assessments conducted at 6 and 12 months (Fig. 1).

**MAS**
No statistically significant differences were observed in any of the patients assessed, either in the baseline examination or in the examinations conducted 6 and 12 months after DBS of the STN (Fig. 2).

**SSI**
No statistically significant differences were found between the scores obtained at baseline (ON medication) and the scores obtained at 6 and 12 months (ON medication-ON stimulation) (Fig. 3).

**Y-BOCS**
The sample assessed showed a statistically significant difference (p < 0.04) in total score on the scale between baseline (ON medication) and the assessment at 12 months (ON medication-ON stimulation), with no statistically significant difference found separately on the obsessions and compulsions subscale. Although these data correspond to a clinical improvement, the assessment conducted reflects the subclinical severity in this area of psychopathology of the sample. However, no statistically significant differences were found when comparing the assessment conducted at baseline (ON medication) with the assessment conducted at 6 months (ON medication-ON stimulation) or between the assessment conducted at 6 months and the assessment conducted at 12 months (Fig. 4).

**OSQ**
The OSQ score at baseline (ON medication) showed that 70.0% of patients (21 patients) fulfilled the *International Classification of Diseases, Tenth Revision*, criteria and 83.3% (25 patients) fulfilled the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria for the diagnosis of insomnia. No patient fulfilled the criteria for hypersomnia in either of the two classifications. At baseline (ON medication), most patients were observed to be unsatisfied with their sleep, another group of 26.7% (8 patients) were at the midpoint, and 26% (6 patients) claimed they were...
satisfied. Regarding the difficulty of obtaining restorative sleep, half of the sample (15 patients) reported having difficulty versus 26.7% who claimed having no difficulty obtaining restorative sleep. Statistically significant differences (p < 0.0001) were obtained when comparing baseline (ON medication) with the results at 6 and 12 months after surgery (ON medication-ON stimulation) as well as for the item “satisfaction with your sleep” (p < 0.0001). No statistically significant differences were obtained when comparing the scores between 6 and 12 months after surgery (ON medication-ON stimulation) (Fig. 5).

**SF-36**

On the SF-36 scale, a direct score > 50 was obtained only in the subscales of pain, social functioning, role-emotional, and mental health of the sample, with both summary scores (physical health and mental health) < 50, which corresponds to low quality of life in these patients at baseline. Statistically significant differences (p < 0.005) were obtained in all subscales when comparing baseline (ON medication) with the results at 6 and 12 months (ON medication-ON stimulation). The direct scores obtained increased in all subscales, > 50 points, which corresponds to a significant improvement in quality of life. No statistically significant differences were observed when comparing the assessments at 6 months with those at 12 months (ON medication-ON stimulation), corresponding to a satisfactory perceived quality of life (Fig. 6).

**Levodopa Dose**

A reduction in the mean daily dose of levodopa was observed, p < 0.0001, between baseline (1,080 mg/day ± 322.8 SDs) and at 6 months (ON medication-ON stimulation) of 575.6 mg/day (53.3%) and at 12 months of 590.3 mg/day (54.7%) (ON medication-ON stimulation).

**UPDRS-III**

The UPDRS-III score at baseline OFF medication was 34.3 points ± 14.2 SDs, and at baseline ON medication was 13.4 points ± 7.6 SDs. Statistically significant differences (p < 0.0001) were observed when comparing the scores obtained in UPDRS-III between baseline OFF medication and the scores obtained at 6 (34.3 versus 21) and 12 months (34.3 versus 20.9) OFF medication-ON stimulation. No statistically significant differences were observed in UPDRS-III when comparing the scores between 6 and 12 months (OFF medication-ON stimulation). Likewise, no statistically significant differences were obtained between baseline ON medication and the scores obtained at 6 and 12 months ON medication-ON stimulation (Fig. 7).

**Active Contact Coordinates**

A mean anterior commissure to posterior commissure (AC-PC) distance of 25.14 mm ± 3.12 SDs was obtained. For the right contact, a lateral distance, X-coordinate, of 11.3 mm ± 1.8 SDs from the AC-PC line, a distance from the mid-ICP, Y-coordinate, of 1.2 mm ± 1.6 SDs behind the ICP and a distance below the AC-PC line, Z-coordinate, of 2.9 mm ± 3.1 SDs were obtained. A voltage of 3.1 (1.2–3.7) volts, a pulse width of 68.1 (60–120) microseconds, and a frequency of 150 (90–185) Hz were used.

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**Fig. 5** Oviedo Sleep Questionnaire (OSQ) and satisfaction with sleep from baseline to 6 and 12 months after DBS of the STN. M12, assessment conducted 12 months after DBS of the STN; M6, assessment conducted 6 months after DBS of the STN.

**Fig. 6** 36-Item Short Form Health Survey (SF-36) subscales from baseline to 6 and 12 months after DBS of the STN. M12, assessment conducted 12 months after DBS of the STN; M6, assessment conducted 6 months after DBS of the STN.

**Fig. 7** Unified Parkinson’s Disease Rating Scale, subscale III (UPDRS-III) (ON/OFF) scores from baseline to 6 and 12 months after DBS of the STN. M12, assessment conducted 12 months after DBS of the STN; M6, assessment conducted 6 months after DBS of the STN; UPDRS-III OFF, Unified Parkinson’s Disease Rating Scale, subscale III when not taking drug treatment; UPDRS-III ON, Unified Parkinson’s Disease Rating Scale, subscale III when taking drug treatment.
For the left contact, an X-coordinate of 10.8 mm ± 2.3 SDs, a Y-coordinate of 0.8 mm ± 1.7 SDs behind the ICP and a Z-coordinate of 3.3 mm ± 2.3 SDs below the AC-PC line were obtained. A voltage of 3.2 (2.0–3.7) volts, a pulse width of 68 (60–120) microseconds, and a frequency of 155 (90–185) Hz were used. No statistically significant differences were obtained between the direct and left active contact coordinates, or between the stimulation parameters.

Discussion

Regarding the variations in psychiatric parameters after DBS of the STN, there is significant controversy given the variability in the results observed in the publications reviewed.\textsuperscript{11,25–28}

MES

A meta-analysis showed a worsening in depressive symptoms in 20 to 25% of patients undergoing DBS of the STN,\textsuperscript{29} with these symptoms related to a series of disorders associated with stimulation of behavioral regions.\textsuperscript{30} In our study, a statistically significant clinical improvement in depressive symptoms was observed in patients undergoing DBS of the STN, passing from moderate severity to mild depression at 6 months (ON medication-ON stimulation) and even absence of depression at 12 months (ON medication-ON stimulation). Therefore, with DBS of the STN, not only do depressive symptoms not worsen, but they improve over the first 6 months and are maintained up to 12 months after DBS. These results are consistent with those of other authors who also obtained an improvement in depressive symptoms after DBS of the STN.\textsuperscript{3,13}

The hypothetical relationship between DBS of the STN and a reduction in levodopa as a possible cause of the increase in depressive symptoms\textsuperscript{31,32} is not borne out in our study. Although the prescribed daily dose of levodopa in patients undergoing surgery was reduced to less than half of the dose prescribed before DBS, depressive symptoms improved. Nevertheless, it must be kept in mind that depression is caused by a confluence of intrinsic and extrinsic biological factors, family factors, and social factors, and it is not just a surgery-related symptom.\textsuperscript{33} However, it appears that the location of the electrode and stimulation in a more ventral position may lead to a worsening of the patient's mood.\textsuperscript{34} We therefore postulate that placement of the electrode in the posterior dorsolateral region of the STN is the most suitable to improve motor symptoms and not to worsen affective symptoms.

MAS

None of the patients enrolled in this study fulfilled the criteria for the diagnosis of manic symptoms in the baseline examination. Likewise, such symptoms have not appeared de novo after DBS of the STN, as shown by the results obtained in the follow-up performed at 6 and 12 months. These results contradict those obtained by some authors who report symptoms of hypomania in 4 to 15% of patients undergoing DBS of the STN.\textsuperscript{35} The literature reviewed suggests that the mania/hypomania induced by DBS of the STN is associated with more ventral-medial placement of the electrode in the STN and with a high stimulation voltage (>3 V).\textsuperscript{36,37} In all of our patients, the active contact was located in the posterior dorsolateral region of the STN.

SSI

One of the most controversial aspects when considering DBS of the STN has been the high rate of postoperative suicide, 12 to 15 times higher than the rate observed in the same age group.\textsuperscript{12,29} Although this high suicide rate is primarily related to DBS of the thalamus and of the globus pallidus interna,\textsuperscript{38,39} the persistence of suicidal ideation is believed to be a distinctive characteristic of depression after DBS of the STN, mainly in patients with a history of depression and anxiety.\textsuperscript{40} Even so, suicide is due to multiple factors, and this possible neurobiological factor (DBS) could play a small part within a wider context.\textsuperscript{29} However, in most of the studies reviewed, psychometric assessment was not performed before surgery, and it is therefore not possible to establish a single relationship between DBS and the high suicide rate observed. None of the subjects enrolled in our study had a score in the baseline examination indicating clinical severity. Likewise, no statistically significant difference was observed on comparing the three assessment time points, baseline, at 6 months, and at 12 months, although a tendency was observed toward a disappearance of suicidal thoughts, possibly related to the improvement in somatic and depressive symptoms.

Y-BOCS

Another of the aspects we studied is the variation in pre- and postoperative obsessive symptoms. Although the patients’ score in the preoperative assessment did not reflect clinical severity, a statistically significant improvement was observed when comparing the baseline assessment (ON medication) with the assessment conducted at 12 months (ON medication-ON stimulation). These results are consistent with those obtained by other authors.\textsuperscript{41–44}

OSQ

It is a demonstrable fact that patients with PD suffer significant sleep disturbances, both in structure and in the duration of sleep. In our patients, a statistically significant clinical improvement in sleep quality was observed between the assessment conducted at baseline and the assessments conducted at 6 and 12 months (ON medication-ON stimulation). Some authors suggested that chronic DBS of the STN improves sleep quality thanks to a reduction in sleep fragmentation and a reduction in the dose of levodopa after surgery.\textsuperscript{45–47}

SF-36

In our study, a statistically significant improvement in quality of life was observed in all subscales and summary components of the psychometric test chosen when comparing the preoperative baseline assessment (ON medication) with the assessments conducted at 6 and 12 months (ON medication-ON stimulation). The only component in which no difference was observed in the various assessments was role-emotional, with the score obtained high at baseline and even higher in the assessments conducted at 6 and
12 months. In line with the results obtained in this study, recent research studies have shown that DBS of the STN significantly improves quality-of-life indicators in patients with PD, including in those who receive only drug treatment, especially in the subscales related to the performance of activities of daily living, functional abilities, emotional well-being, and perception of stigma. Modifications in NMSs are also correlated with changes in quality-of-life parameters, with a significant correlation observed between depressive and anxious symptoms and improved quality of life in patients after DBS of the STN.

**Levodopa Dose**

The mean reduction in the levodopa equivalent dose is 50 to 60% compared with the preoperative mean dose. In our study, the daily dose of levodopa decreased by 53.3% at 6 months and 54.7% at 12 months after DBS of the STN. Although some authors recommend not reducing dopaminergic therapy too suddenly after surgery with DBS of the STN, so that DBS of the STN can, over time, compensate for the reduction in the dose of levodopa, the reduction of levodopa in our study occurred over the first month after surgery with no neuropsychiatric abnormalities observed.

**UPDRS-III**

In our patients, the mean score in UPDRS-III was 34.3 at baseline OFF medication and 13.4 at baseline ON medication; that is, they showed a 60.9% improvement. Comparing the score on the UPDRS-III scale at baseline OFF medication with the situation OFF medication-ON stimulation at 6 and 12 months, improvements of 38.9% (34.3 versus 21) and 39% (34.3 versus 20.9) were obtained, respectively. Comparing the score on the UPDRS-III scale at baseline OFF medication, with the situation ON medication-ON stimulation at 6 and 12 months, improvements of 59.8% (34.3 versus 13.8) and 58.9% (34.3 versus 14.1) were obtained, respectively. All of these improvements were statistically significant (p < 0.0001). If we now compare the score on the UPDRS-III scale at baseline ON medication with the situation ON medication-ON stimulation at 6 and 12 months, we find virtually no changes (13.4 versus 13.8 and 13.4 versus 14.1).

Thus it can be inferred that there is a 60% improvement in UPDRS-III at 12 months after surgery and in the ON medication-ON stimulation situation, which is practically the same as the result obtained for baseline ON medication over baseline OFF medication, but with a 53.3% reduction in the daily dose of levodopa (1,080 mg/day to 489.7 mg/day) (p < 0.0001) and without the side effects induced by levodopa. In a meta-analysis performed in 2006, it was concluded that DBS of the STN produced a 27.5% improvement in UPDRS-III in the OFF medication-ON stimulation situation with respect to the baseline OFF medication situation and with a 55.9% reduction in the levodopa equivalent dose.

One year after surgery, Gan et al obtained a 54.2% reduction in the UPDRS-III scale between the baseline OFF medication situation and the ON medication-ON stimulation situation and a 48.6% reduction in the levodopa equivalent dose. Six months after surgery, Wodarg et al obtained a 30% improvement between baseline OFF medication and the OFF medication-ON stimulation situation. Finally, in a series of 262 patients, Welter et al obtained a 61.8% improvement (38.7 vs 14.8) (p < 0.001) in the UPDRS-III scale between baseline OFF medication and the ON medication-ON stimulation situation. In this series, 19 patients developed hypomania.

**Location of the Stimulation Electrode**

It was recently shown that correct placement of the electrode in the posterior dorsolateral region of the STN is the factor with the greatest influence on good outcomes in DBS of the STN. The imaging method most widely used for visualization of the electrodes is the fusion of preoperative magnetic resonance imaging with postoperative CT scans. In our study, the mean active contact coordinates on both sides were 11 ± 1.7 SDs lateral to the AC-PC line, 1.6 ± 1.7 SDs behind the ICP, and 3.2 ± 2.8 SDs below the AC-PC line. These coordinates usually correspond to contact number 3. Transferring these coordinates to the atlas of Schaltenbrand and Warren showed us that these contacts were within the posterior dorsolateral region of the STN. Several studies have shown that the most active contacts when checking for an improvement in the clinical symptoms of PD were located in the dorsal part or in the dorsolateral part of the STN. Nevertheless, the variability in electrode placement and the small size of the STN may lead to diffusion of the electrical current to adjacent nonmotor structures such as the limbic territory of the STN, causing nonmotor side effects such as postoperative euphoria and hypomania. Episodes of acute hilarity, hyposexuality, mania, and manic psychosis were also reported.

Frankemolle et al indicated that the cognitive and motor impairment associated with DBS of both STNs can be reverted without compromising motor benefits, by optimizing stimulation parameters and thus avoiding spreading of the current to nonmotor regions of the STN. Lalys et al defined the motor region par excellence of the STN as in the posterior dorsolateral part of the STN, but they state that its stimulation is not without complications such as impairment of phonemic fluency. Eisenstein et al reported that the best motor results after DBS occur when the electrode is located in the posterior dorsal region of the STN/zona incerta. Stimulation of this region produces improvements in motor function, mood, and anxiety but a worsening of cognitive function (working memory), although if the stimulation current threshold is reduced, the impairment of cognitive functions is reverted.

Aviles-Olmos et al showed that the best motor results were obtained when the electrodes were located in the posterior dorsolateral part of the STN, where the β oscillatory activity of this nucleus is located. Garcia-Garcia et al showed that the best motor results were obtained via stimulation of the dorsolateral part of the STN and of the area between the subthalamic region, the zona incerta, and the thalamic fasciculus. Abulseoud et al found no significant differences in motor results between patients with psychiatric diseases and those with no psychiatric disease.
However, psychiatric symptoms occurred more frequently in patients undergoing bilateral DBS of the STN and with more medial placement of the electrode. They explain this fact by stating that the electrode placed in the ventromedial region of the STN could cause overactivation of the limbic circuit and consequently cause psychiatric symptoms.

Finally, increased impulsivity was described under agonist therapy as a D2-receptor effect. Frank et al. showed that DBS selectively interferes with the normal ability to slow down when faced with decision conflict. Schuepbach et al. reported no differences for cognitive assessments, changes in mood in favor of neurostimulation, as were the scores on the Brief Psychiatric Rating Scale for overall psychiatric morbidity.

All the patients after DBS decreased the average dose of levodopa up to 54.7% (1,080 ng/day overall psychiatric morbidity). Although the number of cases in our series was limited, DBS views of spouses, family, and caregivers.

**Limitations of the Study**

There were no control groups or randomization. There were a limited number of patients and also a limited follow-up period. An important source of information was the interviews of spouses, family, and caregivers.

**Conclusions**

Although the number of cases in our series was limited, DBS of the STN in patients with PD is associated with an improvement in psychiatric (affective and sleep-wake cycle) symptoms, clinical motor symptoms, and quality of life at 1 year after surgery, as well as a reduction in the dose of levodopa and therefore in levodopa-induced side effects. Further studies and with long-term follow-up are needed to confirm our outcomes because in larger series psychiatric side effects occur that were not observed in this series.

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