Levodopa Withdrawal After Bilateral Subthalamic Nucleus Stimulation in Advanced Parkinson Disease

José L. Molinuevo, MD; Francesc Valldeoriola, MD; Eduardo Tolosa, MD; Jordi Rumia, MD; Josep Valls-Solé, MD; Héctor Roldán, MD; Enric Ferrer, MD

**Context:** Subthalamic nucleus (STN) stimulation may be effective in ameliorating parkinsonian symptoms even to the extent to permit levodopa withdrawal.

**Objectives:** To analyze the efficacy of STN stimulation in patients with Parkinson disease (PD) and to determine if levodopa may be withdrawn after surgery.

**Design:** Before-after trial.

**Setting:** Referral center, hospitalized care.

**Patients:** Fifteen patients with advanced PD.

**Interventions:** Microelectrode-guided bilateral STN high-frequency stimulation.

**Outcome Measures:** Before surgery patients were evaluated in off-medication and on-medication conditions. Dopaminergic drug dosages were reduced after surgery, aiming for complete withdrawal. Six months after surgery, patients were reevaluated in off- and on-medication conditions, with the stimulation turned on and off.

**Results:** Total Unified Parkinson’s Disease Rating Scale (UPDRS) motor score in the off-medication condition improved by 65.9%; and axial symptoms, bradykinesia, rigidity, and tremor improved by 65.8%, 60.4%, 66.1%, and 81.1%, respectively. UPDRS part II scores were reduced by 71.8% and Schwab and England scores improved by 45.3%. Levodopa was withdrawn in 8 patients and the overall levodopa dose was reduced 80.4%. “Off” time was reduced 89.7% and the severity of dyskinesias decreased 80.6% after surgery. All results reached significance (P < .001). Stimulation of the STN achieved antiparkinsonian effect similar to that of treatment with levodopa. No life-threatening adverse effects occurred.

**Conclusions:** Bilateral STN stimulation safely improves all parkinsonian symptoms, decreases or eliminates the need for levodopa, and ameliorates motor fluctuations and dyskinesias. Complete withdrawal of levodopa is feasible with this technique and the overall motor effect of STN stimulation is quantitatively comparable to that obtained with levodopa.

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FUNCTIONAL neurosurgery is a valid therapy to relieve parkinsonian symptoms and drug-induced dyskinesias in patients with advanced Parkinson disease (PD). Unilateral ablative procedures, such as posteroventral pallidotomy, have mainly contralateral effects, and bilateral pallidotomy is typically avoided because it incurs a high risk for severe adverse effects. In contrast, high-frequency deep brain stimulation (HF-DBS) for the treatment of PD is a reversible, adaptable, and safe technique even when applied bilaterally, although serious adverse events can occur. The target for HF-DBS was initially directed toward the thalamus to treat tremor, and subsequently displaced to the internal pallidum. Subthalamic nucleus (STN) blockade was shown to be effective to alleviate parkinsonian symptoms in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated primates. Posteriorly, STN stimulation was performed in humans with success. This technique proved to be effective to ameliorate PD symptoms and dyskinesias. Although several studies have suggested that long-term bilateral stimulation of the STN can produce an antiparkinsonian effect similar to that obtained with levodopa treatment, this has not been adequately assessed, because, in these studies, levodopa had not been withdrawn after surgery. Therefore, the specific effect produced exclusively by STN stimulation has not been evaluated.

The main objective of this study was to analyze the efficacy and safety of bilateral microelectrode-guided STN stimulation in patients with advanced PD expe-
PATIENTS AND METHODS

PATIENTS

Fifteen consecutive patients were operated on between 1997 and 1998 at our institute. All patients met the United Kingdom Parkinson’s Disease Society brain–bank clinical criteria for idiopathic PD.20 Selection criteria were age younger than 75 years and the presence of disabling motor fluctuations and drug-induced dyskinesias refractory to medical therapy adjustments. All patients necessarily showed a good response to a supratherapeutical dose of levodopa. Exclusion criteria were presence of cognitive impairment, major depression, and marked cerebral atrophy on neuroimaging studies.

Patients were 10 men and 5 women, with a mean ± SD age of 60.9 ± 6.8 (range, 52–74) years, mean disease duration of 15.8 ± 9.2 (range, 7–38) years, and mean off-medication Hoehn and Yahr stage of 3.8 ± 0.8 (range, 2.5–5). All patients were treated with levodopa (Table 1); 4 patients also used oral dopamine agonists (pergolide mesylate, 3 mg/d [3 patients] and ropinirole hydrochloride, 6 mg/d [1 patient]) and 2 patients used subcutaneous apomorphine hydrochloride (3 mg two or three times daily).

TABLE 1

<table>
<thead>
<tr>
<th>Levodopa Dose</th>
<th>Amount (mg/d)</th>
</tr>
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<tbody>
<tr>
<td>3 mg</td>
<td>[1 patient]</td>
</tr>
<tr>
<td>6 mg</td>
<td>[3 patients]</td>
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<td>[1 patient]</td>
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SCALES USED FOR CLINICAL EVALUATIONS

Clinical assessments were done following the Core Assessment Program for Intracerebral Transplantations (CAPIT) instructions23 4 days before surgery and 6 months after surgery.

All assessments were performed by means of the Unified Parkinson’s Disease Rating Scale22 (UPDRS), version 3.0. The following items were grouped as “axial symptoms”: arising from a chair, gait, posture, postural reflexes, hypokinesia, facial expression, voice, axial rigidity, and axial tremor. Motor fluctuations were assessed by item 39 of the UPDRS. Patients were also graded according to the Hoehn and Yahr staging system23 and Schwab and England (S/E) scale.24 Dyskinesias were evaluated using the Abnormal Involuntary Movement Scale25 (12 items, maximum score = 48, graded 0–4).

RESULTS

MOTOR SYMPTOMS

Long-term bilateral STN stimulation significantly reduced all motor symptoms 6 months after surgery (Table 2) when comparing off-med scores obtained before surgery with the off-med/on-stim scores after surgery. Total UPDRS part III score decreased by 65.9% (P < .001); axial symptoms, bradykinesia, rigidity, and tremor improved by 65.8%, 60.4%, 66.1%, and 81.1%, respectively (P < .001). Hoehn and Yahr stage changed from 3.8 ± 0.7 before surgery to 1.9 ± 0.5 after surgery (P < .001). Patient’s activities of daily living scores improved markedly as reflected by the UPDRS part II and S/E scores. UPDRS part II scores were reduced by 71.8% and S/E scores improved by 45.3% when compared with the preoperative off-med condition (P < .001), and 28.9% (P < .12) and 14.7% (P < .001), respectively, when compared with on-med condition. The comparison of the off-med/on-stim and off-med/on-stim scores after surgery revealed similar results (Table 3). The mean voltage intensity used was 3.1 ± 0.7 V. Motor scores in basal conditions (off-med vs off-med/on-stim) were not significantly changed after surgery (Table 3).

DOPAMINERGIC MEDICATION REDUCTION

Eight patients had stopped taking any dopaminergic medication 6 months after surgery, and levodopa was withdrawn in all of them for at least 4 months. In patients still taking medication, the mean reduction was superior to 60%
while the stimulator was on (on-med/on-stim) to evaluate
the severity of dyskinesias.

SURGICAL PROCEDURE

All patients gave their informed consent and the protocol
was approved by the local ethical committee. Antiparkin-
sonian medication was withdrawn the night before
surgery. A model G Leksell stereotactic frame was placed
with the patient under local anesthesia. Images through
the region of the intercommissural line were acquired at
1-mm thick slices obtained through cranial computed
tomography. After selection of a slice with the anterior com-
missure and the posterior commissure, the theoretic an-
tomatic target was placed 2 mm posterior, 5 mm ventral to
the midcommissural point, and 12 mm lateral to the in-
tercommissural line. We approached the target with an
anteroposterior angle of 60° with respect to the intercom-
missural line and a sagittal angle of 10°. The stereotactic
coordinates were calculated by means of a computer pro-
gram containing a digitized brain atlas based on the Schalt-
enbrandt and Wahren atlas.26 Using local anesthesia, a single
15-mm burr hole was made in the skull 2 cm from the mid-
line at the coronal suture. Recording of single-unit neuro-
al activity was performed using neurological registering
equipment (Neurorack; TPM Servicio Médicos, Madrid,
Spain). A platinum-iridium microelectrode (extended
microelectrodes, 14-TDSC-CC; FHC Inc, Bowdoingham,
Me) was inserted through the burr hole. Microelectrode re-
cording was started 20 mm above the theoretic target and
conducted by an electronic microdrive device. By means
of the microelectrode recording the discharge pattern of the
neurones of the thalamus, subthalamus, and substantia nig-
ra pars reticulata could be identified. The sensorimotor
area of the STN was distinguished by modification of neu-
ronal activity in response to active and passive move-
ments or palpation and light touch of individual contra-
lateral body parts.27-29 Microstimulation within the STN
(bipolar pulses at 40-80 µA, 300 Hz, and 500- to 1000-
millisecond duration) was applied to determine the thresh-
old for beneficial and side effects. A minimum of 1 and a
maximum of 4 parallel, in the parasagittal and coronal
planes, exploration tracks were needed for localization of the
sensorimotor STN area and its anatomic boundaries.
Patients were induced with brief general anesthesia using
intravenous propofol (2.5 mg/kg) during the procedure
except when their collaboration was needed. Once the sen-
sorimotor area of the STN was determined, an electrode for
long-term stimulation (DBS 3389 electrode; Medtronic, Min-
neapolis, Minn) was inserted at this location. An external
stimulation device connected to the stimulation electrode was
then used to confirm that there were not any limiting side
effects, such as diplopia, tonic contraction of a limb, pares-
theses, dyskinesias, or vegetative symptoms, and that mo-
tor response was adequate. Cranial magnetic resonance im-
ageing was performed in all the patients immediately before
lead implant to rule out hemorrhagic complications and elec-
trode misplacement. Programmable pulse generators (Itrel II,
Medtronic) were implanted in the subclavicular region
ipsilateral to the electrode 1 week after surgery.

STATISTICAL ANALYSIS

To assess the effectiveness of STN stimulation, we compared
the off-med scores obtained before surgery with the off-med/
on-stim scores after surgery, and the off-med/off-stim with
the on-med/on-stim scores obtained after surgery. Scores of
the UPDRS part II (activities of daily living) and evaluation
of the S/E scale, could not be assessed for on-med condition
after surgery in patients without levodopa; consequently, we
only considered for data analysis the off-med/on-stim activi-
ties of daily living scores after surgery. This score was com-
pared with the preoperative on-med and off-med scores. We
also compared preoperative off-med and postoperative off-
med/off-stim scores. To ascertain whether the symptomatic
effect of levodopa was similar to that obtained with STN stimu-
lation, we compared the presurgical on-med with the off-
med/on-stim scores in patients who were free of levodopa
for at least 2 months.

Statistical analysis was performed by means of SPSS-PC
Windows 3.1 version (SPSS Inc, Chicago, Ill). All com-
parisons were done through a paired t test for indepen-
dent data. To avoid a type I error, P = .001 was considered
to indicate statistical significance.

in 6 and 20% in 1. Dopamine agonists were withdrawn in
all patients except one who is still taking pergolide. Two
patients with 12 months’ and 2 patients with 18 months’
follow-up are still without any medication. We tried to re-
introduce levodopa in some of these patients to assess
whether they could further benefit from it, but as they did
not obtain any added useful effect they preferred to re-
main free of levodopa. Overall, the daily levodopa equiva-
 lent dose was reduced 80.4%, from 1338 ± 656 mg/d to
262 ± 332 mg/d (P<.001) in the whole group.

MOTOR FLUCTUATIONS

The 8 patients who were completely free of antiparkin-
sonian drug treatment and 3 patients still taking small
doses of levodopa did not report daytime or nocturnal
symptom fluctuations. The other 4 patients reported brief
“wearing-off” periods characterized by the reappearance
of mild motor symptoms. The UPDRS item that as-
sesses the percentage of the day spent in “off” periods
decreased by 89.7%, from 2.6 ± 1 before surgery to
0.3 ± 0.5 after surgery (P<.001).

DYSKINESIAS

All patients presented peak dose dyskinesias before sur-
gery and none of them showed biphasic dyskinesias. Nine
of the 15 patients were completely relieved of dyskine-
rias after surgery. The remaining 6 patients experienced
only mild, painless choreiform dyskinesias at otherwise
optimal antiparkinsonian stimulation parameters. Three
of these 6 patients were not taking any dopaminergic
medication, and the abnormal movements disappeared
when stimulation intensity was decreased. The severity of
dyskinesias, measured by the Abnormal Involuntary
Movement Scale, decreased by 80.6% after surgery
(P<.001) in the whole group and by 63.7% (P<.001) in the
patients still experiencing dyskinesias.
COMPARISON OF THE EFFECTS OF STN STIMULATION VS LEVODOPA

In the subgroup of patients who were completely free of medication, comparison between on-med UPDRS motor scores and off-med/on-stim scores showed no significant differences, apart from the motor scores obtained for the axial items of the UPDRS (P < .001). By contrast, the comparison of the S/E scale and the Hoehn and Yahr staging system between on-med and off-med/on-stim conditions improved by 16.3% and 32.5%, respectively, after surgery (P < .001). There were no preoperative significant differences in age, disease duration, and disease severity, measured by the UPDRS, S/E, and Hoehn and Yahr scales between patients who were taking levodopa before surgery and those who were not. A Pearson test correlating preoperative and postoperative doses of levodopa (R = 0.16) and a t test comparing preoperative levodopa dose in both groups (P = .46) disclosed no significative differences.

ADVERSE EFFECTS

No life-threatening adverse effects were seen as a consequence of surgery. Transient confusion, disorientation, and abulia were observed during the first 2 weeks after surgery. One patient developed mild postoperative depression, which still persisted at 6 months’ follow-up. Depression was not modified by lead polarity or current intensity changes as described by Bejjani et al. Two patients experienced dysarthria and hypophonia that were intense in one patient and mild in the other.

Table 1. Daily Total Equivalent Levodopa Dose Before and After Surgery

<table>
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<th>Patient No.</th>
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<tr>
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<td>2</td>
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<tr>
<td>15</td>
<td>2550</td>
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</tr>
</tbody>
</table>

Bilateral STN stimulation significantly improved all cardinal symptoms of PD in our patients. This improvement, unlike the presurgical condition during which control of symptoms with levodopa was erratic and intermittent, was consistent and continuous during the whole day. These antiparkinsonian effects of bilateral STN stimulation allowed a complete withdrawal of dopaminergic drugs in more than half the patients and a marked reduction in dosage in the remaining patients. This study confirms previous reports that levodopa reduction is possible after STN stimulation, but is the first one stating that levodopa can be completely withdrawn after STN stimulation in some patients during prolonged periods of time. In addition, the dose reduction in dopaminergic drugs obtained in our patients is higher than that reported in previous studies. This decrease in levodopa use was associated with a reduction of dyskinesias. In consonance with previous reports, side effects were generally minor and tolerable, although this technique may present serious morbidity.

In patients in whom levodopa was withdrawn, we observed that the antiparkinsonian effect of HF-DBS was quantitatively similar to that achieved with levodopa before surgery. The effects obtained with either of both therapies on bradykinesia, rigidity, and tremor were not significantly different; however, all the measures tended to improve in the on-stim condition compared with the on-med condition. The improvement in axial symptoms was significantly greater with STN stimulation than with levodopa. This could be considered to be part of a global improvement when compared with the on-drug condition that could be related to a reduction in dyskinesias after stimulation. In the other patients still requiring levodopa, STN stimulation relieved most of symptoms but some of them were relieved only at the expense of producing bothersome side effects. These residual symptoms were improved by the addition of small doses of levodopa. This group of patients was clinically and demographically similar to the group in which levodopa was completely withdrawn and the preoperative doses of levodopa were also similar in both groups. Since there were not any presurgical differences between these 2 groups of patients, the incomplete response to STN stimulation in patients still needing levodopa after surgery could reflect a suboptimal lead placement.

Motor fluctuations were not present in patients not requiring levodopa after surgery. Some patients who were still taking levodopa stayed in a continuous “on” condition with a smooth motor status, with the combined effect of stimulation and medication. Other patients with mild symptoms when the effect of medication wore off were considered to still experience mild intensity fluctuations. Improvement of motor fluctuations after STN stimulation has been described in 2 previous studies, but in other reports such effect was not clearly stated. The mechanisms favoring the attenuation of motor fluctuations are directly related to the clinical effect of STN stimulation, which is probably associated with the direct and complete inhibitory effect on the subthalamic pallidal excitatory pathway. Therefore, the overactivation of the internal pallidum could be constantly inhibited by STN stimulation bypassing the abnormal pulsatile striatal pharmacological activation exerted through the indirect pathway. The hypothesis is further supported by the fact that some patients did not have any
beneficial effect after taking single doses of levodopa, due to a possible ceiling effect over the dopaminergic responsive symptoms, reflecting a bilateral complete STN blockade. Moreover, positron emission tomographic studies have shown that STN stimulation improves activity of motor association cortex, possibly by reducing inappropriate excitation of the STN on inhibitory pallidothalamic projections.33

Subthalamic HF-DBS was also associated with a marked reduction in peak dose dyskinesias in all patients. In line with the observation that STN blockade can directly induce hyperkinesias,13,15,19,34,35 some patients in whom levodopa had been withdrawn had minimal dyskinesias together with the best clinical effect of stimulation. Consequently, we agree with the common opinion17,19,35,36 that improvement of dyskinesias after surgery is best explained by the reduction of the total daily levodopa dose rather than by a direct HF-DBS effect over the STN37,38 as suggested by others.

In addition to the prolonged symptomatic effects of STN surgery17 on parkinsonian symptoms, some authors have suggested, based on animal models, the possibility that subthalamic HF-DBS could alter the natural history of PD by exerting a neuroprotective effect.39,40 We did not observe significant changes in motor scores when comparing the off-med condition before surgery with off-med/off-stim condition after surgery. Appropriately designed studies should be done to answer the question whether STN stimulation can have neuroprotective properties. Such studies should include a comparison of PD patients with and without STN stimulation and consider that the interval needed for motor symptoms to reappear completely after HF-DBS arrest is not known; therefore, the baseline motor status may not be achieved even after several hours following stimulation arrest.

In summary, bilateral STN stimulation is an effective and generally safe procedure that improves all levodopa-sensitive symptoms, reduces motor fluctuations, and diminishes the need for dopaminergic drugs,
therefore contributing to a marked amelioration in dyskinesias. Neurophysiologic evaluation is mandatory to localize the sensorimotor area of the STN since millimeter accuracy is needed to achieve the best results. Complete withdrawal of levodopa is feasible with this technique in some patients and the overall motor effect of STN stimulation is quantitatively comparable to that obtained with levodopa.

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Reprints: Francesc Valldeoriola, MD, Servei de Neurologia, Hospital Clinic Universitari, Villarreal 170, Barcelona 08036, Spain.

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