Unilateral stimulation of the subthalamic nucleus in Parkinson disease: a double-blind 12-month evaluation study

Isabelle M. Germano, M.D., Jean-Michel Gracies, M.D., Ph.D., Donald J. Weisz, Ph.D., Winona Tse, M.D., William C. Koller, M.D., Ph.D., and C. Warren Olanow, M.D.

Departments of Neurosurgery and Neurology, The Mount Sinai School of Medicine, New York, New York

Object. Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been established as an effective treatment for Parkinson disease (PD). Nevertheless, bilateral surgical procedures can be associated with frequent and severe complications. The aim in the present study was to assess the safety and efficacy of unilateral STN stimulation, and the need for a second procedure.

Methods. Twelve patients with PD underwent unilateral DBS of the STN and were followed up for 12 months. Patients were assessed at baseline and at each visit in a double-blind fashion by analyzing the Unified PD Rating Scale (UPDRS), ambulation speed, and home diaries.

Levodopa-off/stimulation-on UPDRS motor scores were improved by 26 ± 8% (p < 0.05, mean ± standard deviation [SD]) compared with the baseline levodopa-off score; there was a 50% improvement in contralateral features, a 17% improvement ipsilaterally, and a 36% improvement in axial features. The mean ambulation speed increased by 83 ± 44% (p < 0.01, mean ± SD). The medication-on time with dyskinesias was significantly reduced (p < 0.01) and the daily levodopa dose was reduced by 19 ± 6% (p < 0.05, mean ± SD). There were no clinically significant side effects.

Conclusions. Unilateral DBS of the STN is safe and well tolerated, and may provide sufficient benefit so that additional surgery is not required.

Key Words • deep brain stimulation • unilateral stimulation • subthalamic nucleus • Parkinson disease

Parkinson disease is a chronic degenerative disorder of the nervous system. Although levodopa treatment is highly effective, it is associated with long-term motor fluctuations and dyskinesias that significantly hamper the patient’s quality of life.29 Bilateral high-frequency DBS of the STN provides significant amelioration of motor symptoms with reduced motor complications3,10,16,24,32, and has become a standard surgical treatment for PD. Nevertheless, bilateral surgical procedures are associated with an increased risk of complications, and unilateral surgical procedures can provide significant benefit in patients with PD with reduced risks of adverse events.1,21,37 Indeed, in addition to contralateral improvement, ipsilateral and axial improvement have been reported after unilateral pallidotomy,3,21 subthalamotomy,1,37 and DBS of the globus pallidus internus.25 Unilateral DBS of the STN can also be associated with substantial benefits10,27,38 and has not been reported to be associated with the adverse cognitive effects that have been observed after bilateral DBS of the STN.2,3,33,4,1 To evaluate further the safety and efficacy of unilateral DBS of the STN, we performed a 1-year study of unilateral STN stimulation with double-blind evaluations.

Abbreviations used in this paper: DBS = deep brain stimulation; MR = magnetic resonance; PD = Parkinson disease; SD = standard deviation; STN = subthalamic nucleus; UPDRS = Unified PD Rating Scale.

Clinical Material and Methods

Patient Population

This study was conducted with Food and Drug Administration and Internal Review Board approval and is in compliance with the Mount Sinai School of Medicine Internal Review Board rules. Twelve patients with advanced PD complicated by motor symptoms that could not be satisfactorily controlled with medical therapies and who were considered to be candidates for bilateral DBS of the STN were enrolled in the study (Table 1). All patients enrolled in this study had axial and limb symptoms. These were asymmetrical and worse on one side of the body; the STN contralateral to the worse body symptoms received the implant. Inclusion criteria consisted of the following: 1) patient of either sex between 30 and 80 years of age; 2) diagnosis of PD based on the United Kingdom brain1 bank criteria; 3) advanced PD as defined by a motor score greater than 30 on the UPDRS10 and a Hoehn and Yahr17 score greater than Stage III in the practically defined levodopa-off status; 4) more than 20% off time during the waking day, based on the patient’s home diary; and 5) stable doses of antiparkinsonian medications for more than 1 month prior to surgery. Exclusion criteria consisted of the following: 1) dementia or psychiatric problems that would preclude being able to give informed consent; 2) clinically significant medical or labo-
TABLE 1  
Baseline characteristics of 12 patients with advanced PD treated with unilateral DBS of the STN*  

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Duration of PD Preop (yrs)</th>
<th>Resting Tremor</th>
<th>Levodopa (mg/day)</th>
<th>UPDRS III Score off Levodopa</th>
<th>H &amp; Y Stage</th>
<th>Target</th>
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<td></td>
<td>105</td>
<td>3</td>
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* H & Y = Hoehn and Yahr; SEM = standard error of the mean; + = present; 0 = absent.

**Results**

The primary outcome measure for the study was the change in the UPDRS motor score between the off-stimulation state at baseline and the off-medication/on-stimulation state at the 12-month visit. Secondary end points recorded before and after surgery included the mean change in percentage of off time as reported in the patient diaries, the ambulation speed, and the daily levodopa dose. Data were analyzed using the paired Student t-test (two-tailed) for all variables, based on the assumption of a normal distribution. Significance was set at a probability level of 0.05.
UPDRS motor score per item was 1.9 ± 0.2 in the clinically more affected side and 1.6 ± 0.2 in the less affected side. The mean improvement in the UPDRS III score in the levodopa-on state was 45%. The mean medication-off time was 41% of the waking day, and the mean medication-on time was 13% with dyskinesias and 46% without dyskinesias. Patients underwent stereotactic implantation of the stimulation electrode in the STN contralateral to the more affected hemibody (on the left side in nine cases and on the right in three). The electrode position was verified to be in the area of the STN in each case on postoperative MR images (Fig. 1). The stimulation settings are summarized in Table 2.

Nine patients were stimulated using the case as the anode (eight with a monopolar electrode configuration and one with a tripolar configuration [C1C2]), and three had bipolar configurations. The mean stimulation parameters were as follows: amplitude 2.6 ± 0.8 V, pulse width 223 ± 192 μsec, and frequency 183 ± 7 Hz.

Effects of Unilateral STN Stimulation

Following unilateral STN stimulation, there was a mean improvement in the UPDRS motor score of 26 ± 8% between the baseline medication-off state and the medication-off/stimulation-on state at 12 months (p = 0.0015; Fig. 2). When analysis was restricted to contralateral subscores, patients receiving stimulation improved by 50 ± 7% (p = 0.007), ipsilateral subscores improved by 17 ± 8% (p = 0.33), and axial subscores by 36 ± 3% (p = 0.02). Among the axial scores, rising from a chair and postural stability were most improved (Fig. 3). The mean increase in ambulation speed was 83 ± 44% (p < 0.01). Two patients who were unable to walk before surgery recovered this ability after surgery.

Changes in percentage medication-off (poor motor function) and medication-on (good motor function) times based

### Table 2

<table>
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<tr>
<th>Case No.</th>
<th>Electrode Configuration</th>
<th>Amplitude (V)</th>
<th>Pulse Width (μsec)</th>
<th>Rate (Hz)</th>
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<tr>
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Fig. 1. A: Computer-assisted surgical planning based on MR imaging. Intraoperative photographs of the computer screen displaying reformatted coronal (upper left), sagittal (upper right), axial (lower left), and three-dimensional (3D) (lower right) images obtained while planning the target, entry point, and trajectory for a left DBS electrode of the STN. A plate from the Schaltenbrand and Wahren atlas reformatted to fit the patient’s anatomy is superimposed on the triplanar images. B: Postoperative MR images. Photographs of the computer screen displaying reformatted coronal (upper left), sagittal (upper right), axial (lower left), and 3D (lower right) images with a plate from the Schaltenbrand and Wahren atlas reformatted to fit the patient’s anatomy and overlapped to the triplanar images. The permanent DBS electrode is seen in the left STN as a focal signal void (black dot) on the triplanar images; it is indicated by a cylinder in the 3D image.
on home diaries are shown in Fig. 4. Medication-on periods without dyskinesias during the waking day increased from 46 ± 3% to 56 ± 3% (p = 0.08), whereas medication-on periods with dyskinesias were reduced from 13 ± 3% to 5 ± 1% (p < 0.01). Medication-off time was reduced from 41 ± 3% to 36 ± 4% (p = 0.42). Daily sleeping time was increased by a mean of 30 minutes. The mean levodopa daily dose reduction was 19 ± 6% (p = 0.07).

All procedures were well tolerated, and there was no surgical or perioperative occurrence of morbidity or death. Specifically, no patient experienced an intracranial hemorrhage, infarction, or infection, and no patient suffered neurological disability postoperatively. No adverse cognitive effects were observed on clinical examination. There were no side effects related to the stimulator system and no electrode had to be withdrawn or repositioned. No other side effects related to the procedure were noted.

Discussion

We report improvement in parkinsonian motor features that persisted for 12 months after a unilateral DBS of the STN in each of 12 patients with advanced PD who underwent this procedure. Each was considered to be a candidate for bilateral procedures, and in 10 of 12 the benefit associated with the unilateral procedure was sufficient to avoid the need for a second one. Benefits were confirmed by double-blind testing in which patients were randomized into stimulation-on or -off groups. Bilateral DBS of the STN has been shown to be an effective treatment for advanced PD and has been reported to improve the UPDRS motor score in the off period by 30 to 60% and to increase stimulation-on time without dyskinesia. Nevertheless, bilateral intracranial surgical procedures can be associated with clinically significant adverse events that occur far more frequently than with unilateral procedures. In addition, the costs of a surgical procedure and of the implant system are substantial. We observed no clinically significant adverse events with unilateral DBS of the STN in any of the patients presented in this study, and 10 of 12 attained sufficient improvement that they did not require a second surgical procedure. The results of this study indicate that satisfactory benefits can be obtained with unilateral DBS of the STN in many patients with advanced PD, thereby avoiding the costs and risks associated with a second procedure.

Safety of Unilateral Compared With Bilateral Procedures for PD

Adverse events can occur as a result of any intracranial procedure and they include hemorrhage, infection, and neurological deficits caused by local tissue damage. Bilateral...
procedures are associated with an increased risk of side effects, which include the aforementioned adverse events as well as an increased risk of dysarthria, dysphagia, and cognitive impairment. Furthermore, each DBS procedure is associated with side effects related to the implanted stimulator system and to the stimulation itself. Most reported trials of DBS have involved bilateral procedures, reflecting the bilateral nature of PD. In the largest of these studies, 35 bilateral DBSs of the STN were performed in 70 individuals. In that series, serious adverse effects observed during 6 months of follow up included postoperative confusion (10 patients); hemiparesis, infection, and dysarthria (four each); intracerebral hemorrhage, seizures, lead migration, system infection, memory impairment, and hypophonia (three each); and lead break and prolonged confusion (one each). We observed no clinically significant adverse events in our trial, and specifically there was no confusion, dysarthria, or dysphagia.

The reports on the cognitive effects of bilateral DBS of the STN have been inconsistent. In some studies the authors have reported no change or improvement in some cognitive areas, whereas others have reported significant declines in working memory, speed of mental processing, and set switching, particularly in patients older than 69 years. We recently used a specific neuropsychological test battery to study and differentiate the effects on cognition of the surgical procedure and stimulation in 17 patients who underwent bilateral DBS of the STN. In this study, the surgical interventions were found to have affected adversely attention and concentration, verbal learning, naming, and fluency. No cognitive side effects or benefits were associated with STN stimulation itself. In contrast, neuropsychological testing after unilateral procedures reveals only minimal postoperative memory or language deterioration, particularly after left subthalatomy.

In our series, there was no perioperative morbidity, no serious side effects were attributed to the DBS procedure, and no cognitive deficits were observed clinically. Although we studied only a small number of patients, it seems clear that the risks of surgery are substantially reduced after unilateral compared with bilateral DBS of the STN.

One of the disadvantages of unilateral implantation in our study is our inability to compare unilateral with bilateral stimulation in the same patient. On the other hand, one of the advantages is that there has been no surgical procedure, independent of stimulation, performed on the opposite side. Additional multicenter collaboration is needed to optimize the design of further prospective studies focused on the assessment of unilateral compared with bilateral STN stimulation.

Efficacy of Unilateral DBS of the STN

Bilateral DBS of the STN has been reported to provide 30 to 60% improvement in components of the UPDRS III score. Our patients with unilateral DBS of the STN showed a lesser benefit, but nonetheless had meaningful improvement. Their UPDRS scores were improved by 50% on the contralateral side, by 17% ipsilaterally, and by 36% in axial features. Verhagen, et al., published a preliminary study of 25 consecutive patients with PD who were evaluated 4 months after unilateral DBS of the STN. A significant improvement occurred in the UPDRS III score (31%), with the major effects seen contralaterally. Gait was also significantly improved. Similar results were obtained by Kumar, et al., who compared unilateral to bilateral DBS of the STN by turning off one of the stimulators. In their study of 10 patients, unilateral stimulation provided a 25% reduction in off-period parkinsonism, whereas bilateral DBS was associated with a 55% improvement. It thus seems clear that bilateral procedures provide a higher level of efficacy than unilateral procedures, but they are associated with additional risks and costs.

Unilateral pallidal procedures for patients with PD primarily benefit contralateral features, but improvement in ipsilateral and axial features has been noted, although these benefits tend to be temporary, rarely lasting more than 1 year. Deep brain stimulation of the globus pallidus internus provides benefits similar to pallidotomy. Unilateral subthalatomy is reported to provide significant improvement in contralateral tremor, freezing of gait, postural stability, and facial expression. Ipsilateral benefits, when present, were reported to last only a few months. In our study the patients were less severely affected than in other previously reported series on DBS of the STN (the mean baseline UPDRS III score was 42). The symptomatology was asymmetrical, but UPDRS scores on the more affected side were only 20% worse than on the less affected side. Nonetheless, in the majority of cases unilateral DBS of the STN with electrodes implanted contralaterally to the more clinically affected side not only provided the expected contralateral clinical improvement, but also meaningful and sometimes dramatic benefits in axial symptoms such as sitting, gait, and postural stability.

Axial improvement after a unilateral intervention may be related to restoring excitability to the ipsilateral premotor cortex, which may be sufficient to initiate walking and standing movements bilaterally, because 20% of the corticospinal tract runs ipsilaterally to the axial musculature.

Technical Considerations

Our own technique of electrode placement and of setting adjustments may have contributed to our results. Localization of the subcortical nuclei has been performed indirectly based on fixed distances from the anterior commissure—posterior commissure line. Nevertheless, these measurements carry a risk of error because there are substantial interindividual anatomical differences. Advances in MR acquisition techniques allow great visualization of deep brain structures such as the STN. Starr, et al., reported on six cases of subthalamic targeting based on MR imaging visualization of the STN. Similarly, we targeted the STN based on anatomical review of MR images. Intraoperative microelectrode recording was used to confirm the positioning within the STN. Postoperative MR images were obtained in all of our patients to document the placement of the stimulation electrode in the STN.

Postoperatively, the pulse generator was programmed using the maximal stimulation frequency available with the Medtronic programmer (185 Hz) because the effects of DBS of the STN are frequency-dependent. According to the rapid analytic method, the electrode configuration chosen in each case was that providing the maximal amplitude gap between the threshold for beneficial effect (tremor interruption, or muscle twitch in patients with nontremulous
Unilateral subthalamic nucleus stimulation for PD

PD) and the threshold for intolerable adverse effects. The amplitude selected was the highest tolerated within that window. In three of our patients, the thresholds for beneficial effects were sufficiently low to enable the use of a focal field with bipolar settings, thereby minimizing the adverse effects of stimulation.

Conclusions

Our patients underwent unilateral DBS of the STN and had significant improvement after 1 year, but to a lesser extent than has been reported after bilateral DBS of the STN. This improvement was free of serious adverse events, however, and was considered to be of sufficient magnitude in 10 of 12 patients that a second surgical intervention was not recommended. The decision to perform a bilateral procedure in patients with PD is sometimes based on nonmedical reasons because bilateral DBS of the STN has emerged as the standard surgical treatment for advanced PD, and physicians may routinely perform bilateral procedures, often in one stage. Our study results indicate that in some patients with PD, unilateral DBS of the STN may provide satisfactory results and it may not be necessary to perform a second procedure, thereby avoiding the associated risks and costs. It may be that our patients will eventually require a second procedure, but even in this case a prolonged separation between surgical procedures may be an advantage.

References


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