Pallidal vs Subthalamic Nucleus Deep Brain Stimulation in Parkinson Disease

Valerie C. Anderson, PhD; Kim J. Burchiel, MD; Penelope Hogarth, MD; Jacques Favre, MD; John P. Hammerstad, MD

Background: Deep brain stimulation (DBS) of the globus pallidus interna (GPI) and subthalamic nucleus (STN) has been reported to relieve motor symptoms and levodopa-induced dyskinesia in patients with advanced Parkinson disease (PD). Although it has been suggested that stimulation of the STN may be superior to stimulation of the GPI, comparative trials are limited.

Objective: To extend our randomized, blinded pilot comparison of the safety and efficacy of STN and GPI stimulation in patients with advanced PD.

Design: This study represents the combined results from our previously published, randomized, blinded, parallel-group pilot study and additional patients enrolled in our single-center extension study.

Setting: Oregon Health and Science University in Portland.

Patients: Twenty-three patients with idiopathic PD, levodopa-induced dyskinesia, and response fluctuations were randomized to implantation of bilateral GPI or STN stimulators. Patients and evaluating clinicians were blinded to stimulation site. All patients were tested preoperatively while taking and not taking medications and after 3, 6, and 12 months of DBS.

Main Outcome Measures: Postoperatively, response of symptoms to DBS, medication, and combined medication and DBS was evaluated. Twenty patients (10 in the GPI group and 10 in the STN group) completed 12-month follow-up.

Results: Off-medication Unified Parkinson’s Disease Rating Scale motor scores were improved after 12 months of both GPI and STN stimulation (39% vs 48%). Bradykinesia tended to improve more with STN than GPI stimulation. No improvement in on-medication function was observed in either group. Levodopa dose was reduced by 38% in STN stimulation patients compared with 3% in GPI stimulation patients (P = .08). Dyskinesia was reduced by stimulation at both GPI and STN (89% vs 62%). Cognitive and behavioral complications were observed only in combination with STN stimulation.

Conclusion: Stimulation of either the GPI or STN improves many features of advanced PD. It is premature to exclude GPI as an appropriate target for DBS in patients with advanced disease.

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Deep brain stimulation (DBS) of the globus pallidus interna (GPI) and subthalamic nucleus (STN) is being intensely investigated for the management of advanced idiopathic Parkinson disease (PD). Although DBS surgery differs from pallidotomy or subthalamotomy only in the final placement of a stimulating lead, DBS is reversible and is associated with decreased risk of reoperation due to inadequate lesion volume. Most important, bilateral DBS is associated with decreased morbidity compared with procedures that lesion structures bilaterally. A number of studies have shown that bilateral stimulation of both GPI and STN is safe and effective for the management of PD symptoms. For practical and theoretical reasons, STN is thought by many to be the preferred target for DBS in patients with advanced disease. However, comparative studies are limited. In a blinded, randomized pilot study of 10 patients, we found no difference in clinical efficacy between stimulation of STN and GPI after 12 months of DBS. We now report 12-month follow-up results on an extended series of 20 patients randomized to bilateral GPI (10 patients) or STN (10 patients) stimulation.

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METHODOLOGY

Overview

The data presented in this article represent the combined results from our previously published randomized, blinded, parallel-group pilot study and additional patients enrolled in our
The extension study was powered to provide a definitive comparison of GPI and STN stimulation. That study began in October 1998. After 15 patients had been enrolled, the Veterans Affairs/National Institutes of Health cooperative trial of a similar study design (and in which we are participating) was begun, and enrollment in our single-center study was stopped. Since results from the Veterans Affairs/National Institutes of Health trial will not be available for several years, randomized comparisons from which to select stimulation site for patients in the immediate future will be limited. In this context, we believed that presentation of combined data from the 2 studies would provide more insight than analysis of a second small cohort. The present report therefore details combined results from patients enrolled in our previously reported pilot study and the extension trial.

PROCEDURES

The use of human subjects was approved by the Oregon Health and Science University Committee on Human Research, and all patients signed written informed consent. Thirty patients were screened for study participation between January 1996 and September 2001. Of these, 25 met inclusion criteria and were enrolled. A flowchart of the study population is shown in Figure 1. Patients who participated in the pilot study (N = 10) underwent a single randomization to GPI or STN stimulation. Subsequent patients (N = 15) were first randomized (2:1) to immediate surgery or medical management. Those patients who were randomized to medical management and continued to meet inclusion criteria after 6 months of best medical management were then randomized, along with the immediate surgery group, to GPI or STN surgery.

All patients were between 20 and 80 years old and were diagnosed as having idiopathic PD (Hoehn and Yahr stages 3-4 while off medication) with prominent bradykinesia and rigidity. Patients were excluded because of severe mental impairment (as determined by semistructured psychological interview or a Mini-Mental State Examination score < 24), depression (Beck Depression Inventory score > 20), abnormal age-adjusted magnetic resonance image or computed tomogram, or previous surgery for PD or disease of the central nervous system other than PD.

Patients had extensive prior exposure to anti-Parkinson medications. All patients were being treated with levodopa at study entry and had been taking a stable dose of anti-Parkinson medications using the Unified Parkinson’s Disease Rating Scale (UPDRS). Dyskinesia was rated in 6 body parts by a 4-point scale (24-point maximum). Activities of daily living were assessed by part II of the UPDRS. Neurologic status was assessed 3, 6, and 12 months after implantation with DBS on and medications on and off (providing an assessment of the effects of DBS and combined DBS and levodopa). Patients enrolled in the extension study were also assessed with DBS turned off (20-30 minutes) and medications on and off (effects of levodopa and baseline disease) at each time point. All evaluating neurologists and patients were blinded to the stimulation site. In the extension study, the evaluating neurologist was also blinded to medication status.

SURGERY

Patients were assigned to GPI or STN treatment groups by simple randomization. Bilateral electrodes were implanted stereotactically in a single operation, as previously described. Initial targeting was based on magnetic resonance imaging (T1 and fast spin echo-inversion recovery), with the midline, midcommissural point and anterior commissure–posterior commissure (AC-PC) plane serving as reference. Physiologic confirmation was obtained intraoperatively by passive movement of the contralateral wrist and elbow during stimulation at 50 and 100 Hz. In GPI patients, proximity to the optic tract and internal capsule was assessed by low-frequency (2-Hz) macrostimulation. The procedure was then repeated on the second side. In the final 13 patients, microelectrode recording (MER) was also performed using a single microelectrode and techniques similar to those described previously. In 1 patient, 5 parallel microelectrodes were advanced simultaneously to the GPI target (vide infra). After verification of target location, the quadripolar DBS electrode (model 3382 or the equivalent model 3387; Medtronic Inc, Minneapolis, Minn) was inserted and fixed to the skull.

Patients underwent a 5- to 10-day screening trial of DBS in the General Clinical Research Center after implantation of stimulating leads using external pulse generators. All patients showed at least 20% improvement in UPDRS motor score in response to DBS alone or in combination with levodopa. Permanent internal pulse generators (Itrel II or Soletra; Medtronic) were implanted in a second procedure. After implantation, pulse generators were initially programmed at settings that afforded maximum symptom relief during trial. Stimulation frequency was set at 130 Hz or, if tremor was present, 185 Hz. Monopolar stimulation was generally used, although in some patients, bipolar stimulation provided better symptom control. Stimulation adjustments were made as necessary by a neurologist (P.H.) or neurosurgeon (J.F.) unblinded to stimulation site. Mean charge density in the GPI group increased from 5.3 to 8.4 microcoulombs (µC) per square centimeter per pulse (62%)
A total of 25 patients (19 men and 6 women) were enrolled. One patient failed to complete baseline evaluation because of cardiac complications. In an effort to examine the relative efficacy of DBS and medical management, all patients in the extension study were randomized twice: first to medical management or immediate surgery (1:2) and then to surgical target. Because only 2 patients had been randomized to medical management at the time the study was stopped, no group analysis was possible. However, motor symptoms of 1 patient improved after 6 months of medical management, and she no longer qualified for study inclusion. Demographic characteristics of all 23 patients randomized to GPi or STN stimulation are presented in Table 1. There was no difference between the GPi and STN stimulation patients in most variables, including age, mood, and severity of motor symptoms, although disease duration was longer in the STN stimulation group. Of the 23 randomized patients, 1 died of causes unrelated to DBS after 3 months, 1 experienced unexplained, severe PD progression after 6 months of DBS therapy, and 1 had an intraoperative ischemic stroke with persistent neurologic deficit. These patients were considered further only in analyses of complications. Overall, complete 12-month follow-up data were available for 10 GPi and 10 STN stimulation patients.

**MOTOR AND COGNITIVE EFFECTS OF GPi AND STN STIMULATION**

Stimulation improved the baseline off-medication UPDRS motor score at each follow-up (P < .001). The effect of stimulation site on motor scores is shown in Figure 2. After 12 months, off-medication scores were improved by 39% in the GPi stimulation group and 48% in the STN stimulation group. Between-group differences in 12-month off motor scores were not significant (Table 2). The effect of DBS on individual motor symptoms was assessed by relevant items of the UPDRS and is shown in Figure 3.26 Twelve months of either GPi or STN stimulation improved baseline rigidity, bradykinesia, tremor, and axial symptoms (speech, gait, posture, and postural stability). Bradykinesia tended to improve more with STN stimulation (Table 2). Axial symptoms, assessed collectively as the sum of the appropriate UPDRS items,27 also tended to improve more in STN stimulation patients, although differences were smaller (40% vs 44%). Decreased motor signs translated into improved activities of daily living in both groups. As measured by UPDRS (part II), 12-month activities of daily living while patients were not taking medication improved by 23% in

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**Table 1. Baseline Demographic and Clinical Variables in 23 Randomized Patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>GPI Group (n = 11)</th>
<th>STN Group (n = 12)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54 ± 12</td>
<td>61 ± 9</td>
<td>.13</td>
</tr>
<tr>
<td>Symptom duration, y</td>
<td>10.3 ± 2</td>
<td>15.6 ± 5</td>
<td>.002</td>
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<tr>
<td>Hoehn and Yahr stage (0-5)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Not taking medication</td>
<td>4.0 (4-4.5)</td>
<td>4.0 (3-4)</td>
<td>.48</td>
</tr>
<tr>
<td>Taking medication</td>
<td>2.5 (2-3)</td>
<td>2.5 (2-3)</td>
<td>.68</td>
</tr>
<tr>
<td>Total UPDRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not taking medication</td>
<td>92 ± 31</td>
<td>88 ± 20</td>
<td>.88</td>
</tr>
<tr>
<td>Taking medication</td>
<td>44 ± 27</td>
<td>43 ± 15</td>
<td>.31</td>
</tr>
<tr>
<td>Motor UPDRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not taking medication</td>
<td>51 ± 22</td>
<td>49 ± 13</td>
<td>.73</td>
</tr>
<tr>
<td>Taking medication</td>
<td>22 ± 19</td>
<td>20 ± 11</td>
<td>.81</td>
</tr>
<tr>
<td>Dyskinesia rating scale</td>
<td>8.5 ± 5.3</td>
<td>11.2 ± 5.9</td>
<td>.23</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>11 ± 7</td>
<td>14 ± 6</td>
<td>.21</td>
</tr>
</tbody>
</table>

Abbreviations: GPI, globus pallidus interna; STN, subthalamic nucleus; UPDRS, Unified Parkinson’s Disease Rating Scale.

*Values are presented as mean ± SD or median (interquartile range).
†P values for comparisons between groups based on analysis of variance or Wilcoxon rank-sum tests.
all patients, with no difference between the GPi and STN stimulation groups (Table 2).

The effect of long-term stimulation was evaluated in 11 patients by assessment of motor response with medications and DBS off. Although we observed a small decrease (improvement) in motor score from $44 \pm 14$ at baseline to $38 \pm 20$ after 12 months of DBS, the change was not statistically significant ($P = .29$, paired t test).

Neither on-medication motor score nor any individual symptom score was improved by 12 months of DBS (Figure 2 and Table 3). There was no site dependency of individual symptom response as rated by the UPDRS, although UPDRS bradykinesia tended to show greater improvement in the STN stimulation group ($P = .09$, paired t test of differences). On-medication UPDRS activities of daily living were not improved by the addition of either STN or GPi stimulation, nor were there any significant site-dependent changes in cognitive or behavioral test results after 12 months of stimulation.

**EFFECTS OF LONG-TERM STIMULATION ON LEVODOPA DOSE AND RESPONSE**

After 12 months of DBS, the levodopa requirement was reduced by 38% in STN stimulation patients compared with 3% in the GPi stimulation group ($P = .08$, paired t test across groups). In 2 STN stimulation patients, levodopa use was completely discontinued, although it was reintroduced at lower levels than baseline after several months of DBS. The response of motor symptoms to levodopa after the addition of DBS was evaluated in 10 patients (5 in the GPi stimulation group and 5 in the STN stimulation group), after turning the stimulation off for 20 to 30 minutes. On-medication/off-DBS motor scores were increased (worsened) compared with baseline at 3- and 6-month follow-up. By 12 months, on-medication/off-DBS motor scores had deteriorated 112% (range, 47%-194%) from $14.5 \pm 5$ to $31.7 \pm 13$ compared with baseline on. Worsening was noted in both the STN and GPi stimulation groups, with no significant group effect.

Dyskinesia was assessed by the dyskinesia rating scale and patient-scored visual analog scale and was improved in both groups (89% vs 62% for the GPi and STN stimulation groups; Table 3). Dyskinesia was also assessed in 10 patients with levodopa on and stimulation on and off. After 3 months of STN stimulation, dyskinesia severity was improved by 88% regardless of whether stimulators were off (Figure 4A) or on (Figure 4B). In contrast, GPi stimulation patients required active stimulation for dyskinesia improvement. After 3 months, GPi stimulation patients showed a 67% reduction with stimulators turned on and a 23% increase when stimulators were turned off. After 12 months of DBS, though, dyskinesia was improved in both groups with or without active stimulation.

**COMPLICATIONS**

There was 1 intraoperative complication. During advancement of 5 parallel microelectrodes to the GPi target, a 42-year-old patient experienced an intraoperative ischemic stroke. Postoperatively, the patient was hemiparetic and aphasic. His condition improved slowly during subsequent months, but neurologic deficits persist. Additional surgery-related complications were experienced by 3 patients and included infraclavicular hematomas that resolved without intervention and 1 patient who required prophylactic antibiotics after difficulty tunneling the extension wire during generator implantation. One patient (GPi) experienced a device-related complication, an extracranial lead fracture, after falling while...
gardening approximately 6 months after implantation. Surgical removal and replacement with an identical lead were without complication.

Perioperative complications were common among STN stimulation patients. Three STN stimulation patients experienced mild delirium that resolved over several days. Two patients experienced transient anxiety (nervousness, restlessness, tension), and another experienced hallucinations that resolved with reduction of the levodopa dose. Cognitive changes were also noted in 2 STN stimulation patients. In the first patient, short-term memory deficits, difficulty concentrating, and apathetic mood were noted within weeks of surgery that persisted throughout therapy. In the second patient, decline in cognitive function and increased parkinsonian symptoms developed during therapy despite best medical efforts. She was treated with intravenous antibiotics for recurring urinary tract infections. However, by 12-month follow-up, the patient was severely bradykinetic and rigid, had difficulty swallowing, and was unable to communicate. No perioperative changes in cognition or mood were noted among GPi stimulation patients. Mild visual field defects were reported by 1 patient in the GPi stimulation group that resolved by adjustment of stimulation parameters.

Previous case series and single-arm studies have shown improvement with either GPi or STN stimulation. Indeed, in the largest study to date, the DBS for PD Study Group compared motor function in 96 STN and 34 GPi stimulation patients and found that 6 months of DBS improves baseline off-medication motor score by 40% to 50% regardless of target. Our data, collected in a randomized, blinded fashion, are consistent with these results and further suggest that even in the longer term, 12 months and beyond, the difference in the extent to which off-medication motor symptoms are improved by stimulation at either site is small. We also did not find any evidence for a substantially better response with STN vs GPi stimulation.

COMMENT

<table>
<thead>
<tr>
<th>Table 3. Changes in Neurologic Function During Combination Levodopa and Deep Brain Stimulation*</th>
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<tbody>
<tr>
<td><strong>Variable</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td>UPDRS motor</td>
</tr>
<tr>
<td>Rigidity</td>
</tr>
<tr>
<td>Tremor</td>
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<tr>
<td>Bradykinesia</td>
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<tr>
<td>Axial symptoms</td>
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<tr>
<td>Activities of daily living</td>
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<tr>
<td>Dyskinesia severity rating</td>
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</tbody>
</table>

Abbreviations: GPi, globus pallidus internus; STN, subthalamic nucleus; UPDRS, Unified Parkinson’s Disease Rating Scale.

*Values are presented as mean ± SD or median (interquartile range).
†P values based on repeated-measures analysis of variance or Wilcoxon signed-rank test comparison of baseline and 12-month scores.
‡Not calculated; only 3 patients had baseline tremor while taking medication.

Figure 4. Mean ± SEM dyskinesia severity during (A) levodopa only and (B) combination levodopa and deep brain stimulation in globus pallidus interna stimulation (black bars, n=5) and subthalamic nucleus stimulation (white bars, n=5) patients.
tient numbers, our data suggest that STN stimulation is likely to improve off-medication bradykinesia (and, possibly, axial symptoms) more than GPi. This result is consistent with the retrospective study by Krack et al., which found that bradykinesia was improved by 70% to 80% by STN stimulation compared with 30% to 40% in the patients with GPi stimulation (P < .05), and the study by Volkman et al., which found that baseline bradykinesia was significantly improved (P < .001) by 12 months of STN but not GPi stimulation.

It is also clear that medications are likely to be reduced only in combination with STN stimulation. Nevertheless, dyskinesia is markedly reduced by stimulation at either GPi or STN, although it is likely that the mechanism of dyskinesia reduction may be different at the 2 sites. After 3 months of DBS, active STN stimulation is not required for dyskinesia reduction. In contrast, in GPi patients, dyskinesia is reduced only during active stimulation. In addition, long-term GPi stimulation may, as suggested by Bejjani et al., produce long-term changes in dopaminergic systems. Our observations of (1) 12-month dyskinesia reduction in GPi stimulation patients even when DBS is off and (2) worsened on-medication motor score with long-term stimulation are consistent with this idea. Clearly, much more work will be required to clarify the effects of long-term DBS on basal ganglia circuits and levodopa response.

The randomized, blinded design of our trial permits comment on the relative safety of DBS at either site. Based on our experience with this small group of 23 patients, it appears that, in the hands of an experienced surgeon, serious surgical risks of bilateral implantation of DBS leads in STN stimulation are no greater than of placement in GPi stimulation. However, the increased frequency of postoperative delirium and confusion in STN stimulation patients is consistent with some increased vulnerability of STN stimulation and surrounding tissue to DBS surgery. Perioperatively, this tends to make management of STN stimulation patients more difficult. Management is further complicated by the levodopa dose reduction after STN but not GPi implantation. Anxiety, in particular, is fairly common in STN stimulation patients during this period.

This study has limitations. First, the number of patients is small. With only 23 patients, the present study is likely to find statistically significant differences only if the effect size is large. Some of the differences between targets that are statistically insignificant here may be significant in the context of a larger trial. Second, MER was not used to localize the target in all patients. Because commercial recording systems were unavailable at the time of study initiation, the Food and Drug Administration disallowed MER in the first 10 patients. By the time the extension study was started, approved MER systems were available and approval for use in the study was granted. Even in patients in whom MER was used, techniques were not completely consistent. In 12 patients, a single microelectrode was advanced only enough times (typically 1 or 2) to confirm target coordinates. There were no intraoperative complications in these patients. The 1 intracranial complication that occurred was attributed to the use of 5 parallel microelec trodes that were advanced simultaneously to the GPi target. Although some groups report excellent results with this device, our experience reflects the well-known principle that each trajectory through the brain increases the surgical risks. Indeed, the DBS for PD Study Group concluded that the number of microelectrode passes was positively associated with an increased risk of intracranial bleeding. Our current use of MER due to DBS procedures is limited to 1 or 2 passes of a single microelectrode, if possible, with online processing to extract as much information as possible from each recording site. The third limitation of this study is that only a few patients were examined with DBS off, and in those the duration that DBS was off before symptom measurement was not strictly defined. In most cases, we waited 20 to 30 minutes after turning off DBS before measuring symptoms. This delay was chosen because it is a manageable time frame in the context of a clinic visit. Nevertheless, this time may be insufficient for the effects of stimulation to subside completely. Indeed, it now appears that stimulation, particularly at GPi, may require up to 24 hours to completely wear off. Similarly, there was no strict protocol for management of DBS parameters or medications after DBS implantation. Rather, we optimized both in concert based on clinical experience, with parameters and dose adjusted while assessing the interactions between the two. Although we recognize that strict management guidelines would improve study reproducibility, we have found that the wide range of stimulation parameter and dose combinations makes such guidelines problematic. Therefore, in our study we relied on our clinical knowledge of the effects of DBS and medications to optimize results. Finally, although we did not examine them in a rigorou s way, our study suggests that cognitive and behavioral changes are more common after STN than GPi implantation. Although changes were generally mild and transient, in 2 STN stimulation patients they tended to persist. The relative effects of GPi and STN stimulation on cognition and behavior bear additional attention in future controlled trials.

At this point, it appears that stimulation at either STN or GPi improves off-medication motor scores and levodopa-induced dyskinesia for at least 1 year, and there is no clear superiority of STN over GPi stimulation. Indeed, our comparison of GPi vs STN stimulation suggests that selection of a stimulation site should be influenced by symptom profile. Although GPi stimulation may be better for the patient with dose-limiting dyskinesia, STN stimulation may be better for the younger patient with prominent bradykinesia.

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Author Contributions: Study concept and design: Anderson, Burchiel, and Favre. Acquisition of data: Anderson, Hogarth, Favre, and Hammerstad. Analysis and interpretation of data: Anderson, Favre, and Hammerstad. Drafting of the manuscript: Anderson and Hammerstad. Critical revision of the manuscript for important intellectual content: Burchiel, Favre, and Hammerstad. Statistical analysis: Anderson and Favre. Obtained funding: Burchiel and Favre. Administrative, technical, and material support: Hogarth and Hammerstad. Study supervision: Anderson, Burchiel, and Hammerstad.
REFERENCES