Comparison of Pallidal and Subthalamic Nucleus Deep Brain Stimulation for Advanced Parkinson’s Disease: Results of a Randomized, Blinded Pilot Study

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OBJECTIVE: Deep brain stimulation (DBS) of the globus pallidus internus (GPI) and subthalamic nucleus (STN) has been reported to be effective in alleviating the symptoms of advanced Parkinson’s disease (PD). Although recent studies suggest that STN stimulation may be superior to GPI stimulation, a randomized, blinded comparison has not been reported. The present study was designed to provide a preliminary comparison of the safety and efficacy of DBS at either site.

METHODS: Ten patients with idiopathic PD, l-dopa-induced dyskinesia, and response fluctuations were randomized to implantation of bilateral GPI or STN stimulators. Neurological condition was assessed preoperatively with patients on and off l-dopa and on DBS at 10 days and 3, 6, and 12 months after implantation. Patients and evaluating clinicians were blinded to stimulation site throughout the study period. Complete follow-up data were analyzed for four GPI patients and five STN patients.

RESULTS: When off-l-dopa, both GPI and STN groups demonstrated a similar response, with approximately 40% improvement in Unified PD Rating Scale motor scores after 12 months of DBS. Rigidity, tremor, and bradykinesia improved in both groups. In combination with l-dopa, Unified PD Rating Scale motor scores were more improved by GPI stimulation than by STN stimulation. On-l-dopa axial symptoms were clinically improved in the GPI but not the STN group. l-Dopa-induced dyskinesia was reduced by DBS at either site, although medication requirement was reduced only in the STN group. There were no serious intraoperative complications among patients in either group.

CONCLUSION: Pallidal and STN stimulation appears to be safe and efficacious for the management of advanced PD. A larger study is needed to investigate further the differences in symptom response and the interaction of l-dopa with stimulation at either site. (Neurosurgery 45:1375–1384, 1999)

Key words: Deep brain stimulation, Globus pallidus, Parkinson’s disease, Stereotaxy, Subthalamic nucleus

Deep brain stimulation (DBS) has been developed as an alternative to ablation of basal ganglia structures for the management of advanced Parkinson’s disease (PD) (3, 4, 10). Although the surgical procedures differ only in the final placement of a lesion or stimulating lead, DBS offers a number of advantages over ablation, including reversibility and decreased risk of reoperation because of inadequate lesion volume. In addition, bilateral DBS may be associated with decreased morbidity as compared with procedures that lesion structures bilaterally (8, 27, 37).

Bilateral DBS of the globus pallidus internus (GPI) (14, 15, 32, 33, 40) and subthalamic nucleus (STN) (3, 20, 23, 26, 29) is under active investigation in patients with advanced idiopathic disease. Although most reports focus on a small number of patients with relatively short-term follow-up periods, results to date suggest that bilateral stimulators can be safely implanted in the GPI and STN and that stimulation of either structure can improve the cardinal features of the disease as well as l-dopa (LD)-induced dyskinesia.

Primarily because of the reduced LD requirement, several groups have suggested recently that STN stimulation may be superior to GPI stimulation in the management of PD (7, 19, 23). However, a randomized, blinded comparison of stimulation at the two sites has not been performed. We report here the first prospective, randomized study of the relative safety and efficacy of bilateral pallidal and STN stimulation in the management of advanced PD.
PATIENTS AND METHODS

Ten patients (age, 56 ± 13 yr; range, 42–71 yr) were enrolled in the study between January 1996 and November 1997. All patients were diagnosed with idiopathic PD (Hoehn and Yahr off-LD Stage III–V) with prominent bradykinesia and rigidity. Tremor, if present, was a minor feature of the disease. Exclusion criteria included severe mood disturbance or dementia (as determined by semistructured psychological interview), low intelligence (Kaufman Brief Intelligence Test [17]) score <80), abnormal age-adjusted magnetic resonance imaging or computed tomographic scan, significant seizure history, previous surgery for PD (thalamotomy, pallidotomy, DBS, or fetal tissue implantation), or supraspinal central nervous system disease other than PD.

All patients had extensive prior exposure to anti-Parkinson’s medications and had been on a stable dosage of current anti-Parkinson’s medications for at least 1 month before surgery. At the time of enrollment, all patients were being treated with LD, and the majority experienced dose-limiting dyskinesia and/or fluctuations. In addition to LD, three patients were taking a dopamine agonist (pramipexole, 3 mg/d; ropinirole, 15 mg/d; or pergolide, 2 mg/d), and two were taking an anticholinergic (benztrapine, 3.5 mg/d; or trihexyphenidyl, 6 mg/d). One patient was receiving amantadine (200 mg/d) in addition to LD. The study was approved by the Oregon Health Sciences University Committee on Human Research, and all patients signed informed consent.

Patients were assessed preoperatively on and off medications, using the Unified PD Rating Scale (UPDRS) (12) and the Hoehn and Yahr Scale (16). Off-LD assessments were made 2 to 3 hours after waking to avoid sleep benefit, and before the first morning dose of LD (the “practically defined off period”). Severity of dyskinesia was rated by body part using a 24-point scale (24). The Schwab and England (30) Activities of Daily Living score was also evaluated. A neuropsychological test battery was administered preoperatively with the patient on LD. Neuropsychological functions that were assessed included: visuomotor processing (Symbol Digits Modalities Test [34]); memory (Controlled Oral Word Association Test [5, 35], Hopkins Verbal Learning Test [6], and Memory Assessment Scale: Names and Faces [41]); attentional capacity (Digit Span [38]); cognitive impairment (Cognitive Difficulties Scale [28]); auditory span (Sentence Repetition [22]); and mood (Beck Depression Inventory [1]).

Ten days and 3, 6, and 12 months after implantation, neurological status was reassessed with DBS on and LD on and off. Both the evaluating neurologist and the patient were blinded to stimulation site throughout follow-up. Postoperative neuropsychological testing was performed at 3, 6, and 12 months of follow-up with DBS and LD on.

Surgery

Patients were selected for GPi or STN treatment groups by simple random assignment. In all patients, bilateral electrodes were implanted stereotactically under local anesthesia in a single operation, with slight modification of previously described techniques (3). Magnetic resonance imaging (T1 and fast spin echo-inversion recovery) was used to determine initial targets, with midline, midcommissural point, and anterior commissure-posterior commissure plane serving as references. Because no microelectrode has been approved for routine use in the United States, microelectrode recordings were disallowed by the Food and Drug Administration under this experimental protocol. Therefore, electrophysiological recordings were not used to refine target coordinates. Physiological confirmation of the target, however, was provided by low-frequency (2 Hz) macrostimulation, which allowed an assessment of electrode position relative to the internal capsule and optic tract (31). Passive movement of the contralateral wrist and elbow during stimulation at 50 and 100 Hz was used to assess the effect of stimulation on rigidity. After confirmation of target location, a quadripolar DBS electrode (Model 3382; Medtronic, Inc., Minneapolis, MN) was inserted and fixed to the cranium (13). The procedure was then repeated on the second side.

All patients then underwent a 5- to 10-day screening trial of DBS with stimulation provided via external pulse generators. The dose of LD was allowed to vary during the trial, as necessary, to increase patient comfort. Initially, stimulation parameters were chosen to provide optimal unilateral symptom control, with bilateral stimulation programmed after sequential optimization of unilateral response. In general, the effect of DBS on motor symptoms was assessed off-LD, with the effect of on-LD-induced dyskinesia assessed afterward at settings that produced good off-LD response. Stimulation was assessed at a variety of bipolar contact combinations, and voltage and/or pulse width were varied at each combination. Final stimulation parameters were chosen on the basis of improvement of the patient’s most disabling symptom and an absence of stimulation-induced sensory symptoms. All patients responded favorably to stimulation during the trial, as assessed clinically, and received implants of permanent Itrel II internal pulse generators (Medtronic).

After implantation, pulse generators were initially programmed to settings that afforded maximal symptom relief during the trial. Bipolar stimulation was used throughout the follow-up period to provide a more localized stimulation volume (11). Stimulation frequency was 185 Hz in all patients except one, whose symptoms were adversely affected at frequencies above 30 Hz. Among all patients, the mean voltage and pulse width were 2.8 ± 0.8 V (range, 1.0–4.0 V) and 158 ± 35 microseconds (range, 120–210 μs) at 10 days and 3.1 ± 1.0 V (range, 1.4–4.5 V) and 190 ± 76 microseconds (range, 120–330 μs) after 12 months of therapy. In general, charge density requirements increased very little among STN patients during the 12 months of follow-up (mean increase, 0.96 ± 2.15 microcoulombs [μC/cm²]/pulse). In contrast, the charge density required to maintain symptom control tended to increase among patients with GPi implants (mean increase, 5.12 ± 4.72 μC/cm²/pulse). A similar increase in charge density after prolonged GPi stimulation has been reported by others (14, 15).

Statistical analysis

The primary outcome measure was the motor subscale of the UPDRS (Items 18–31) in the stimulation on and medica-
tions on and off conditions. Secondary measures included individual UPDRS subscores of rigidity, bradykinesia, tremor, postural stability, and gait, as well as dyskinesia intensity, as assessed by the dyskinesia rating scale. Differences in between-group changes after 12 months of DBS were compared using analysis of variance or, for nonparametric data, the Wilcoxon rank sum (Mann-Whitney) test. Within-group differences in preoperative and 12-month scores were compared using a paired t test or the Wilcoxon signed-rank test.

P values were calculated at the 0.05 significance level in two-tailed tests. Although the number of comparisons made here strictly demands correction of the P value, the goal of this study was not to make definitive statements of statistical significance. Rather, the study was designed as a pilot to determine whether, in a small number of patients, evidence of differences in response to GPi and STN stimulation exists that warrants further investigation within the context of a larger clinical trial. As such, the danger of using a 0.05 significance level with multiple comparisons and declaring a false-positive significant is at least as great as the danger of declaring a false-negative and overlooking a difference that may be significant in a larger population.

RESULTS

Ten patients (7 male, 3 female) were randomized to bilateral implantation of GPi or STN electrodes. Comparison of baseline scores reveals no significant difference between groups with respect to any variable shown in Table 1, although STN patients tended to be older and have less severe motor symptoms than GPi patients. One patient died of causes unrelated to stimulation after 3 months of therapy and was evaluated further only in analyses of complications. Complete 12-month follow-up data are available for four GPi and five STN patients.

Neurological response: off-LD

Figure 1A shows the off-LD UPDRS motor scores for the GPi (n = 4) and STN (n = 5) groups preoperatively and at each follow-up interval. After 12 months of DBS, off-LD motor scores tended to be lower in the STN group (P = 0.11; t test). However, the percent improvement over baseline scores after 12 months was comparable in each group, with 39 and 44% improvement in GPi and STN groups, respectively (P = 0.71; repeated measures multivariate analysis of variance).

TABLE 1. Preoperative Demographic and Clinical Variables a

<table>
<thead>
<tr>
<th>Variable</th>
<th>GPi Group (n = 4)</th>
<th>STN Group (n = 6)</th>
<th>P Value b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>46.5 ± 11</td>
<td>62.8 ± 12</td>
<td>0.06</td>
</tr>
<tr>
<td>Symptom duration (yr)</td>
<td>10.6 ± 2</td>
<td>13.6 ± 5</td>
<td>0.34</td>
</tr>
<tr>
<td>Hoehn and Yahr stage (0–5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off-L-dopa</td>
<td>4.0 (4.0–4.8)</td>
<td>4.0 (3.9–4.0)</td>
<td>0.92</td>
</tr>
<tr>
<td>On-L-dopa</td>
<td>2.5 (2.3–3.0)</td>
<td>2.3 (2.3–3.0)</td>
<td>0.81</td>
</tr>
<tr>
<td>Total UPDRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off-L-dopa</td>
<td>113 ± 42</td>
<td>85 ± 12</td>
<td>0.37</td>
</tr>
<tr>
<td>On-L-dopa</td>
<td>66 ± 35</td>
<td>49 ± 16</td>
<td>0.63</td>
</tr>
<tr>
<td>Motor UPDRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off-L-dopa</td>
<td>67 ± 24</td>
<td>49 ± 12</td>
<td>0.14</td>
</tr>
<tr>
<td>On-L-dopa</td>
<td>38 ± 26</td>
<td>24 ± 14</td>
<td>0.24</td>
</tr>
<tr>
<td>Dyskinesia rating scale</td>
<td>9.5 ± 6.7</td>
<td>13.3 ± 5.4</td>
<td>0.34</td>
</tr>
</tbody>
</table>

a GPi, globus pallidus internus; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale. Plus-minus values are means ± standard deviation. Values with parentheses represent medians (interquartile range).

b P values for comparisons between groups based on analysis of variance or Wilcoxon signed-rank tests.

FIGURE 1. Mean (± standard error of the mean) UPDRS motor scores for GPi (●; n = 4) and STN (○; n = 5) groups preoperatively (time 0) and after 10 days and 3, 6, and 12 months of DBS. A, off-LD; B, on-LD. All postoperative assessments were made on-DBS.
TABLE 2. Off-medication Changes in Neurological Function after 12 Months of Globus Pallidus Internus or Subthalamic Nucleus Deep Brain Stimulation*

<table>
<thead>
<tr>
<th>Variable</th>
<th>UPDRS Item(s)</th>
<th>Maximal Value</th>
<th>Preoperative/12-Mo Score</th>
<th>Change after 12 Mo</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>GPI Group (n = 4)</td>
<td>STN Group (n = 5)</td>
<td>GPI Group (n = 4)</td>
</tr>
<tr>
<td>Rigidty</td>
<td>22</td>
<td>20</td>
<td>13.0 ± 5.7</td>
<td>9.4 ± 2.9</td>
<td>-4.8 ± 3.8c</td>
</tr>
<tr>
<td></td>
<td>8.3 ± 4.1</td>
<td>5.0 ± 2.0</td>
<td>3.3 ± 2.2</td>
<td>2.0 ± 2.8</td>
<td>[37%]</td>
</tr>
<tr>
<td>Tremor</td>
<td>20 + 21</td>
<td>28</td>
<td>12.3 ± 10.2</td>
<td>7.6 ± 6.8</td>
<td>-9.0 ± 10.1</td>
</tr>
<tr>
<td></td>
<td>3.3 ± 2.2</td>
<td>2.0 ± 2.8</td>
<td>25.2 ± 5.9</td>
<td>19.2 ± 4.0</td>
<td>-6.10 ± 0.8d</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>23–26</td>
<td>32</td>
<td>19.3 ± 5.2</td>
<td>14.4 ± 5.1</td>
<td>[24%]</td>
</tr>
<tr>
<td></td>
<td>5.8 ± 2.0</td>
<td>2.5 ± 4.0</td>
<td>29 ± 4</td>
<td>2 (2.0–2.5)</td>
<td>-1 (0.3–1.8)</td>
</tr>
<tr>
<td>Gait</td>
<td>30</td>
<td>4</td>
<td>2 (1.3–2.8)</td>
<td>1 (0–2.0)</td>
<td>[0.10]</td>
</tr>
<tr>
<td>Postural stability</td>
<td>30</td>
<td>4</td>
<td>2 (1.5–3.8)</td>
<td>2 (2–2.5)</td>
<td>-1.8 (0.3–3)</td>
</tr>
<tr>
<td>Speech</td>
<td>18</td>
<td>4</td>
<td>1.5 (1.0–2.0)</td>
<td>2 (0.5–2.0)</td>
<td>[0 (0–1.5)]</td>
</tr>
<tr>
<td>Disease stage (Hoehn and Yahr [16])</td>
<td>43</td>
<td>5</td>
<td>4 (4.0–4.8)</td>
<td>4 (3.8–4.0)</td>
<td>-1 (1–1.8)</td>
</tr>
<tr>
<td>ADL (Schwab and England [30])</td>
<td>44</td>
<td>100</td>
<td>41 ± 26</td>
<td>46 ± 15</td>
<td>26 ± 18c</td>
</tr>
<tr>
<td></td>
<td>68 ± 19</td>
<td>82 ± 8</td>
<td>26 ± 18</td>
<td>36 ± 15</td>
<td>[63%]</td>
</tr>
</tbody>
</table>

* GPI, globus pallidus internus; STN, subthalamic nucleus; UPDRS, Unified Parkinson’s Disease Rating Scale; ADL, activities of daily living. Plus-minus values represent means ± standard deviation. Values with parentheses represent medians (interquartile range). Values in brackets represent percent change from baseline. Negative changes in all UPDRS scores except ADL reflect improvement in function. Positive changes in ADL represent improvement.

a P values were derived by repeated measures multivariate analysis of variance or ordinal logistic regression and denote the overall significance of intergroup differences after 12 months of DBS.

b P value <0.10 for preoperative to 12-month paired comparison.

c P values from paired t test or Wilcoxon signed-rank test denote change from preoperative score and are <0.05.

Overall, the clinical effect of stimulation at either site was smaller when LD was on. In our study, stimulation of both GPI and STN produced little or no additional improvement in rigidity, gait, or posture over that produced by LD alone (Table 3). Of the three cardinal signs, bradykinesia showed the most significant improvement when DBS was combined with LD, particularly among the GPI group (P = 0.005; repeated measures multivariate analysis of variance). As shown in Tables 2 and 3, speech was not clinically improved by GPI or STN stimulation, either on- or off-LD. Finally, when LD was on, the addition of stimulation at either GPI or STN produced little (10–15%) additional improvement in activities of daily living.

Memory, attention, and visuomotor processing, as measured by the neuropsychological battery described above, were unchanged after 12 months of DBS. However, among all patients, the Cognitive Difficulties Scale, which measures everyday inefficiencies caused by lapse of memory or attention, was improved, compared with on-LD baseline scores (P = 0.02; Wilcoxon signed-rank test). In addition, the Beck Depression Inventory score improved 49% among all patients, from 14.3 ± 6.2 at baseline to 7.3 ± 3.2 after 12 months of DBS (P = 0.02; Wilcoxon signed-rank test). There was no between-group difference in any neuropsychological test results after 12 months of stimulation. Similarly, the change over baseline neuropsychological function was not different after 12 months of GPI or STN stimulation.
Medication use

Figure 2 shows the 24-hour LD intake at baseline and throughout the follow-up period. Preoperative LD intake was slightly higher in the GPi group (856 ± 681 mg [GPi] versus 729 ± 360 mg [STN]), although baseline differences were not statistically significant (P = 0.75; t test). After 12 months of DBS, preoperative LD intake was decreased by 51% in the STN group, to 360 ± 307 mg (P = 0.03; paired t test). Two patients in the STN group discontinued LD completely after the addition of DBS. In contrast, LD intake was unchanged by GPi stimulation, with a mean daily dose of 903 ± 603 mg after 12 months of GPi stimulation (P = 0.93; paired t test). A comparable reduction in LD requirement after the addition of STN (21, 23), but not GPi (18, 25), stimulation has been reported previously.

LD-induced dyskinesia intensity was improved after 12 months of stimulation at either site (Table 3). Among STN patients, preoperative dyskinesia was reduced by 67% (P = 0.03; paired t test), consistent with decreased LD intake. The GPi group also experienced a 47% improvement over baseline dyskinesia, which, although not statistically significant (P = 0.18; paired t test), was clinically important. Therefore, it seems that DBS at either GPi or STN improves dyskinesia, although the mechanism may be very different at the two sites.

Complications

There were no serious intraoperative complications of DBS electrode placement in either GPi or STN. Macrostimulation before final electrode placement revealed that initial target

TABLE 3. On-medication Changes in Neurological Function after 12 Months of Globus Pallidus Internus or Subthalamic Nucleus Deep Brain Stimulation

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<tr>
<th>Variable</th>
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<th>P Valueb</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>GPi Group (n = 4)</td>
<td>STN Group (n = 5)</td>
<td>GPi Group (n = 4)</td>
</tr>
<tr>
<td>Rigidity</td>
<td>22</td>
<td>20</td>
<td>8.3 ± 4.6</td>
<td>4.2 ± 3.7</td>
<td>-2.8 ± 2.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.5 ± 3.5</td>
<td>3.2 ± 2.5</td>
<td>[34%]</td>
</tr>
<tr>
<td>Tremor</td>
<td>20 + 21</td>
<td>28</td>
<td>4.5 ± 8.3</td>
<td>2.2 ± 4.9</td>
<td>-4.3 ± 7.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.3 ± 0.5</td>
<td>0.2 ± 0.4</td>
<td>[96%]</td>
</tr>
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<td>Bradykinesia</td>
<td>23–26</td>
<td>32</td>
<td>17.5 ± 7.3</td>
<td>13.0 ± 5.6</td>
<td>-6.5 ± 0.6d</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>11.0 ± 7.7</td>
<td>10.8 ± 6.4</td>
<td>[37%]</td>
</tr>
<tr>
<td>Gait</td>
<td>29</td>
<td>4</td>
<td>1 (0.3–2.5)</td>
<td>1 (0.5–1.0)</td>
<td>-1.0 (0.3–1.8)</td>
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<td></td>
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<td></td>
<td>0 (0–0.8)</td>
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<td>0 (0–0.8)</td>
<td>0 (0–0.5)</td>
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<td>Speech</td>
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<td>4</td>
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<td>1 (0–2.0)</td>
<td>0 (0–0.8)</td>
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<td></td>
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<td></td>
<td>1 (0–1.0)</td>
<td>2 (0–2.5)</td>
<td></td>
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<tr>
<td>Dyskinesia (dyskinesia</td>
<td>24</td>
<td></td>
<td>9.5 ± 6.7</td>
<td>11.6 ± 3.7</td>
<td>-4.5 ± 6.1</td>
</tr>
<tr>
<td>rating scale)</td>
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<td></td>
<td>5.0 ± 5.8</td>
<td>3.8 ± 3.2</td>
<td>[47%]</td>
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<tr>
<td>Disease stage (Hoehn and</td>
<td>43</td>
<td>5</td>
<td>2.5 (2.0–3.0)</td>
<td>2.5 (2.0–3.0)</td>
<td>-0.3 (0–0.9)</td>
</tr>
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<td>Yahr [16])</td>
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<td>2 (2.0–2.4)</td>
<td>2 (2–2.8)</td>
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<tr>
<td>ADL (Schwab and England)</td>
<td>44</td>
<td>100</td>
<td>80 ± 14</td>
<td>78 ± 8</td>
<td>8 ± 15</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>88 ± 5</td>
<td>90 ± 7</td>
<td>[10%]</td>
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</table>

*GPI, globus pallidus internus; STN, subthalamic nucleus; UPDRS, Unified Parkinson’s Disease Rating Scale; ADL, activities of daily living. Plus-minus values represent means ± standard deviation. Values with parentheses represent medians (interquartile range). Values in brackets represent percent change from baseline. Negative changes in all scores except ADL reflect improvement in function. Positive changes in ADL represent improvement.

b P values were derived by repeated measures multivariate analysis of variance or ordinal logistic regression and denote the overall significance of intergroup differences after 12 months of DBS.

c P value <0.10 for preoperative to 12-month paired comparison.

d P values from paired t test or Wilcoxon signed-rank test denote change from preoperative score and are <0.05.
DISCUSSION

In a previous comparison of GPI and STN stimulation, Krack et al. (19) retrospectively assessed the effect of bilateral GPI and STN stimulation in 13 young-onset PD patients. After 6 months of DBS, the off-LD UPDRS motor score was improved by 39% in patients with GPI stimulation and 71% in the STN group. In the only other comparison, Kumar et al. (21) described results from 14 PD patients, 8 with GPI (4 unilateral, 4 bilateral) and 6 with STN (5 bilateral, 1 unilateral) stimulation. Mean UPDRS off-LD motor score was improved by 27% after 3 months of GPI stimulation and by 41% after 1 to 6 months of STN stimulation. Our GPI group results are identical to those of Krack et al. and only slightly higher than those observed by Kumar et al. However, the 44% improvement in our patients after 1 year of STN stimulation, although similar to that reported by Kumar et al., is substantially less than the 71% reported by Krack et al. Whether this difference is due to variation in study design (prospective versus retrospective, randomized versus consecutive, blinded versus unblinded), patient selection (age, disease severity and duration), clinical methodology (location of the DBS electrode, stimulation parameters), or other factors awaits further investigation.

We also observed that the off-LD motor function of patients in either group was improved to within 10% of the preoperative on-LD score after 12 months of DBS. This result suggests that after the addition of DBS, patients functioned as well with DBS alone as they did preoperatively when LD was on. Since this study was originally designed as a pilot study of active GPI and STN stimulation, we did not systematically examine UPDRS changes in the absence of DBS. Therefore, we do not know whether the improved off-LD condition is caused by a gradual adaptation of basal ganglia circuitry or is an immediate consequence of surgery (a microlesion effect). Although the latter are usually of short duration, surgical effects lasting more than 1 year have been reported after implantation of thalamic stimulators (36).

Our data confirm previous reports that STN stimulation does little to improve on-LD motor function (19, 23). However, in GPI patients, we observed a positive interaction between DBS and LD such that the combination of GPI stimulation and LD was better than either alone. A similar result has been reported recently (15, 40). In our study, GPI patients also retained a good response to DBS/LD throughout 1 year, such that the GPI group on-LD motor scores, which were 37% higher (worse) than STN scores preoperatively, were indistinguishable from the on-LD/on-DBS scores of the STN group after 12 months of DBS (Fig. 1B). This result is in contrast to the retrospective report of Krack et al. (19) demonstrating no improvement in GPI patients’ on-LD motor function after 6 months of DBS. Although the precise reason for the difference between this result and that of our own study is unclear, it has been suggested that the response to combination GPI/LD therapy may depend on stimulation parameters, especially the electrode contact(s) (2, 18). Stimulation by inferior contacts seems to produce the best anti-dyskinetic effect, but it also may inhibit the anti-akinetic effect of LD. Our general practice was to use bipolar stimulation between the middle contacts, which may have avoided the LD-inhibitory effect. However, we did not systematically test this hypothesis.

Chronic effects of stimulation are also important clinically. Our data suggest that stimulation at either the GPI or STN site may improve PD symptoms and that, at either site, the clinical response is sustained for at least 1 year. However, the effect of more prolonged stimulation was not systematically examined in the present study. In two previous reports, good response has generally been noted during the first 2 years of GPI stimulation (15, 33). However, a decreased efficacy was recently reported among six patients during the second year of GPI stimulation, despite attempts to optimize response by adjustments of stimulation parameters (14). This latter result is consistent with our own clinical impression that the response of some patients, particularly those with GPI stimula-
tion, tends to deteriorate during the second year of therapy. Very little is known regarding the effects of 2, 3, or more years of STN stimulation. In the only report to date, total UPDRS scores were improved after 1 year and remained significantly improved for 10 patients after 3 years of STN stimulation (39). These results raise the possibility of a differential response to GPi and STN stimulation that is clinically observable only in the long term (>1 yr).

In the present study, simultaneous bilateral implantation of GPi and STN electrodes proved to be a safe procedure, with no serious intraoperative complications. Specifically, there were no intracranial hemorrhages or infection. One lead fracture in one patient occurred subsequent to a fall. Replacement of the lead was performed without complication. The only significant perioperative complication during the study was transient delirium in two patients before activation of the DBS systems. The delirium lasted 1 to 2 days and resolved without sequelae after LD dose reduction. Interference with the output of the impulse generators was the most annoying complication and occurred on several occasions. It is presumed that electromagnetic interference by metal and theft detectors was responsible in most cases.

We conclude that long-term DBS of GPi or STN is safe and efficacious for many features of PD, including gait and postural stability. Compared with our experience with bilateral pallidotomy (9), DBS appears to be at least as efficacious and is without the attendant complications of bilateral ablative procedures. Clinical differences between patients with GPi and STN implants are small after 1 year, although there seems to be a trend toward greater off-LD improvement in patients with STN stimulation. In combination with LD, additional improvement as a result of DBS is small and is indistinguishable between groups after 12 months. However, our data suggest that chronic stimulation of GPi may improve symptoms in combination with LD more than chronic LD/STN stimulation. By far, the major on-LD difference, however, is the reduction in LD requirement among patients with STN implants. This dose reduction probably accounts for the greater improvement in dyskinesia observed in the STN group. Taken together, these results suggest that the mechanism of interaction between LD and DBS may be very different at the two sites.

A larger comparative study is needed to establish conclusively whether there is an important difference in efficacy between GPi and STN stimulation and to determine whether some symptoms respond better to stimulation of one target or another. It will also be important to examine the chronic effects of long-term (>1 yr) stimulation at either site and to explore further the interaction between DBS and LD. Such studies should increase our understanding of basal ganglia function and clarify the role of GPi and STN stimulation as therapy for advanced PD.

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REFERENCES


This is a very important and well-performed study comparing deep brain stimulation (DBS) in the pallidum with that in the subthalamic nucleus (STN) for advanced Parkinson’s disease (PD). Unfortunately, it has two very serious design flaws. The first is the small number of patients involved. One of the tasks of randomization is obtaining two study groups that are not significantly different from each other. This study does that, but the mean age of the two groups is very different, and although not statistically significant, the P value of 0.06 certainly suggests a trend in that direction. Age is an extremely important parameter and one that has been consistently found to correlate with improved response to surgery for movement disorders. There is a very serious problem with a β Type II error (the potential of not finding a significant difference when, in fact, a significant difference exists). Differences between the two treatment groups could be as large as 80%, and it is possible that no significant difference would be identified in this study. According to our preliminary experience with DBS in these two sites (3), 122 randomized patients are required to identify a 10% difference with 0.95 power and a 10% dropout rate.

The other major flaw is that this study did not include a systematic evaluation of the patients in the absence of DBS, both “on” and “off” l-dopa therapy. As the authors suggest, there are probably important differences in the efficacy of l-dopa in combination with stimulation at the two different targets. Without knowing the level of function off-DBS stimulation, it is difficult to make many of the important comparisons on which further understanding of the effect of DBS at the two different sites will ultimately depend.

Despite these shortcomings, the study of DBS using a prospective randomized trial with standardized outcome tools and independent neurological evaluations is an extremely important study design. It is very time consuming and expends a great deal of resources. Nevertheless, the value of such studies is such that they have become the “gold standard” for all of medicine. Surgery, especially neurosurgery, has been slow to take up this concept, and I congratulate the authors for their effort. It must be emphasized that the authors label this work a pilot study. There is a clear need for this type of randomized trial. As the authors indicate, previous studies by Krack et al. (1) and Kumar et al. (2) represent biased and therefore potentially flawed data. Nevertheless,
many members of the neurosurgical community are willing to crown the STN as the site of choice for DBS placement. The most important parameter is how well patients fare on stimulation and on L-dopa therapy, and these results seem to be similar in the current study. Scientific proof, however, will require a great deal more effort.

In summary, there is a clear need for a large-scale study to randomly assess DBS for pallidal PD and STN stimulation for advanced PD. These studies must be performed as carefully as the authors have performed the current pilot study. Only by studying a large number of patients over a long period of time can some of the efficacy questions be answered. In addition to our own National Institutes of Health-sponsored study, there is at least one Veterans Administration-sponsored study, which continues their study and then provides a follow-up report. I would encourage the authors to continue their study and then provide a follow-up report.

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This is a well-organized and well-executed prospective randomized study of Gpi and STN stimulation in patients with PD. Of 10 patients entering the study, complete 12-month follow-up data were available for 4 patients with implantation of bilateral Gpi electrodes and 5 patients with bilateral STN electrodes. These two groups were compared at 3-month follow-up intervals, on and off medication, using the Unified PD Rating Scale, Hoehn and Yahr Scale, Schwab and England Activities of Daily Living scores, as well as neuropsychological tests. The authors found that the procedures could be performed safely and there was little difference in the clinical result between the two groups after 12 months. I agree with their final conclusion: they need more patients and longer follow-up.

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The article by Burchiel et al. is, as stated by the authors, the first randomized prospective trial comparing the efficiency of Gpi stimulation with that of STN stimulation in advanced PD. This type of study is of major importance at a time when health care costs and decision making no longer allow us to submit patients to a large variety of surgical or therapeutic procedures without knowing precisely their respective merits and what indications are best suited for each. In the treatment of advanced stages of PD, we are currently in a favorable situation, because the question of the efficacy of DBS has been positively settled.

The purpose of this article is not to demonstrate the efficacy of Gpi and STN stimulation, which currently is widely accepted, but to compare two surgical opportunities that can be offered to patients in a similar situation. These two opportunities arise from the basic facts that both targets are efficient, both are accessible through a common surgical procedure (the difference being only a matter of coordinates within a range of a few millimeters), and the surgical risks of both procedures have been shown to be very similar. However, the roles of the two targets are not exactly identical, and this might logically introduce some specific differential effects. Their sizes are quite different, which introduces different spatial variability. Furthermore, the magnetic resonance imaging visibility is not the same, which introduces differences in surgical practicability. Thus, comparisons are needed and should address subsequent questions: are the final clinical outcomes significantly different to justify the choice of one target versus the other? Are the differences, if any, specific to some clinical signs, which would warrant different indications for these two targets, according to the patient’s clinical profile? Are the differences due to anatomic subdivisions of the target that would warrant a specific effort to localize these places and implant them selectively?

The article by Burchiel et al. addresses most of these questions. Although the numbers are small, conclusions have been drawn from a carefully designed study, which was extremely well analyzed and may serve as a basis for larger studies to clarify some points. This study may suggest several considerations. Although a larger and longer study is needed to confirm it, the overall benefit for the patients seems to be better with STN stimulation than with Gpi stimulation. This may be due to several factors, the first being that these targets correspond to different structures occupying different places in the organizational scheme of the basal ganglia. The STN is upstream from the Gpi, it projects onto the substantia nigra pars reticulata, and, not surprisingly, it may therefore trigger a different cascade of events than the Gpi or any other target.

It is more important to ask whether the comparison between the Gpi and STN is logically valid. The STN is a small

structure that probably is almost entirely involved when stimulated, whereas the larger size of the Gpi allows the expression of effects that could be more dependent on the anatomo-physiological organization of the Gpi and could explain observed differences between series. This difference may also warrant a search for better intraoperative targeting based on this knowledge, which in large part is still being acquired. One may progress along this way in human patients by a careful correlation between the position of the electrodes and the observed effects. It was not the purpose of the article by Burchiel et al., nor of this comment, to debate the technical methods for surgical implantation. The important point is to know (even more in the Gpi but also in the STN) where an observed effect has been induced. This is why the comments in this article about lower electrodes as compared with upper ones, as discussed in the article by Krack et al. (1), or about bipolar stimulation with the medical electrodes, or about the use of bipolar instead of monopolar stimulation, have to be carefully considered. Lower versus upper positioning is still meaningful, as the global positioning of electrodes is fairly reproducible at the anatomic level but becomes meaningless at the physiological level, where slight variations may account for totally different effects. We expect that progress in postoperative imaging in the next millennium will provide us with accurate knowledge of the position of the stimulating electrode, whereas we have to acknowledge, uncomfortable as it may be, that currently we cannot state for sure where we are placing the electrodes.

This could also partially explain the main discrepancy between this article and that of Krack et al. (1) about the differential benefits of STN and Gpi stimulation. In fact, the results for Gpi are comparable, but the STN results in this study are lower than those in the study by Krack et al. This could be due to the choice of young-onset patients, instead of random parkinsonian patients, in the study by Krack et al. However, this observation of a better effect with STN stimulation, as compared with Gpi stimulation, has also been the case for other Gpi patients, whose scores did not remain stable, and has justified our current attitude in favor of reimplantation in the STN for some of our previously Gpi-implanted patients who are not so well as their STN-implanted counterparts.

The difference might also be due to our lower skills in Gpi implantation, but this would not explain why most of our STN patients have higher scores than those reported in this study or scores similar to those reported in the study by Krack et al. In the article by Burchiel et al., in the on-L-dopa situation, there is no improvement with STN stimulation, whereas there is improvement with Gpi stimulation. It is not clearly stated whether, as in our study, this finding is related to the major effect of Gpi stimulation, L-dopa-induced dyskinesias, as in pallidotomies, whereas STN stimulation reduces L-dopa-induced dyskinesias only because the L-dopa dose has been significantly lowered, owing to the significant effect of the triad symptoms. The authors do not comment on the elevation of the L-dopa dose in Gpi patients; this is not significant in their numerical data, but the trend is visible in their Figure 1 and corresponds to our observations on a larger number of patients, as the average elevation of L-dopa in the Gpi group is about +15%, whereas it is approximately −50% in the STN group.

This study leads to important conclusions, or suggestions of conclusions, on the value of a limited series. It demonstrates that a well-designed and carefully conducted study in one group may lead to interesting conclusions and reinforces my personal opinion that these small studies should be performed more often and are better than large multicenter studies. Multicenter studies have, as their unique and only advantage, the possibility of evaluating on the community level the average result of a procedure practiced at a large scale on a large number of patients. This is important in terms of general health care management but has poor scientific value in detecting subtle anatomo-physiological features, which are eliminated by the large discrepancies between surgical practices, and even more so when surgical procedures are considered.

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