Long-term follow up of bilateral deep brain stimulation of the subthalamic nucleus in patients with advanced Parkinson disease

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Object. The use of deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been associated with a marked initial improvement in individuals with advanced Parkinson disease (PD). Few data are available on the long-term outcomes of this procedure, however, or whether the initial benefits are sustained over time. The authors present the long-term results of a cohort of 25 individuals who underwent bilateral DBS of the STN between 1996 and 2001 and were followed up for 1 year or longer after implantation of the stimulator.

Methods. Patients were evaluated at baseline and repeatedly after surgery by using the Unified Parkinson’s Disease Rating Scale (UPDRS); the scale was applied to patients during periods in which antiparkinsonian medications were effective and periods when their effects had worn off. Postoperative UPDRS total scores and subscores, dyskinesia scores, and drug dosages were compared with baseline values, and changes in the patients’ postoperative scores were evaluated to assess the possibility that the effect of DBS diminished over time.

In this cohort the median duration of follow-up review was 24 months (range 12–52 months). The combined (ADL and motor) total UPDRS score during the medication-off period improved after 1 year, decreasing by 42% relative to baseline (95% confidence interval [CI 35–50%], p < 0.001) and the motor score decreased by 48% (95% CI 42–55%, p < 0.001). These gains did diminish over time, although a sustained clinical benefit remained at the time of the last evaluation (41% improvement over baseline, 95% CI 31–50%; p < 0.001). Axial subscores at the time of the last evaluation showed only a trend toward improvement (p = 0.08), in contrast to scores for total tremor (p < 0.001), rigidity (p < 0.001), and bradykinesia (p = 0.003), for which highly significant differences from baseline were still present at the time of the last evaluation. Medication requirements diminished substantially, with total medication doses reduced by 38% (95% CI 27–48%, p < 0.001) at 1 year and 36% (95% CI 25–48%, p < 0.001) at the time of the last evaluation; this decrease may have accounted, at least in part, for the significant decrease of 46.4% (95% CI 20.2–72.5%, p = 0.007) in dyskinesia scores obtained by patients during the medication-on period. No preoperative demographic variable, such as the patient’s age at the time of disease onset, age at surgery, sex, duration of disease before surgery, preoperative drug dosage, or preoperative severity of dyskinesia, was predictive of long-term outcome. The only predictor of a better outcome was the patient’s preoperative response to levodopa.

Conclusions. In this group of patients with advanced PD who underwent bilateral DBS of the STN, sustained improvement in motor function was present a mean of 2 years after the procedure, and sustained reductions in drug requirements were also achieved. Improvements in tremor, rigidity, and bradykinesia were more marked and better sustained over time than improvements in axial symptoms. A good preoperative response to levodopa predicted a good response to surgery.

Key words • subthalamic nucleus • deep brain stimulation • Parkinson disease • long-term outcome

Deep brain stimulation of the STN results in a dramatic initial improvement in motor function and dyskinesia, and reduces drug dosage requirements in medically intractable patients with PD. Studies have demonstrated a 60 to 80% reduction in motor disability and levodopa-induced complications, and a 40 to 80% decrease in drug dosage requirements in the months following surgery.

Abbreviations used in this paper: ADL = activities of daily living; DBS = deep brain stimulation; PD = Parkinson disease; PIGD = postural instability and gait disturbance; STN = subthalamic nucleus; UPDRS = Unified PD Rating Scale.

The long-term benefits and adverse effects of DBS of the STN have not yet been established. Authors of recent studies have suggested that early benefits in motor function are sustained 2 to 3 years after the procedure; however, other authors have indicated that the procedure may cause significant adverse effects including cognitive decline (especially in executive function), depression, and significant hypophonia. These authors highlight the need for more complete data on long-term outcomes in patients who have undergone DBS of the STN to optimize medical decision making regarding the use of this procedure. We present data on long-term outcome after DBS of the STN in a cohort of individuals who underwent this procedure at our institution.
Clinical Material and Methods

Patient Population

The study cohort represented a subset of 53 individuals who underwent bilateral DBS of the STN at Toronto Western Hospital between 1996 and 2001. Of these, 28 patients were excluded from the present analysis. These patients were excluded on the basis of previous neurosurgical procedures (11 patients), lack of follow-up review because their residence was far away (five patients), follow-up time less than 12 months (10 patients), a skin infection resulting in lead explantation (one patient), or inactivation of stimulation 2 months after the procedure because of a negligible benefit that was possibly due to suboptimal lead placement (one patient). Of the 25 remaining patients with 1 or more years of follow up, eight are participants in an ongoing multicenter study evaluation of a DBS device (data to be reported elsewhere).

All patients underwent microelectrode-guided, simultaneous bilateral DBS of the STN as described in detail elsewhere.12 Informed consent was obtained from each patient before surgery in accordance with the Declaration of Helsinki, and the procedure was approved by the University Health Network (University of Toronto) Ethical Review Board. Postoperative MR images confirmed appropriate lead placement.20 Programming began 2 to 3 weeks after in-Board. Postoperative MR images confirmed appropriate

Measurements of Disease Status

All patients were evaluated at baseline and at follow-up visits by following the protocol of the Core Assessment Program for Intracerebral Transplantation.13 This protocol incorporates the UPDRS,4 which is used to measure ADL (UPDRS Part II) and motor function (UPDRS Part III). Dyskinesia was also assessed using the Dyskinesia Rating Scale. At every evaluation the dosage of antiparkinsonian medication required by the patient was recorded; levodopa equivalents were calculated in a manner described elsewhere.7

Evaluations were made while the antiparkinsonian medication was in effect (medication-on period) and following overnight withdrawal from medication (medication-off pe-

TABLE 1
Characteristics of patients for whom long-term follow-up review was available after implantation of a deep brain stimulator in the STN

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>total no. of patients</td>
<td>25</td>
</tr>
<tr>
<td>no. of female patients (%)</td>
<td>10 (40)</td>
</tr>
<tr>
<td>patient age at disease onset*</td>
<td>43.8 ± 9.6</td>
</tr>
<tr>
<td>patient age at surgery*</td>
<td>57.2 ± 11.7</td>
</tr>
<tr>
<td>duration of disease before surgery in yrs*</td>
<td>13.4 ± 4.3</td>
</tr>
<tr>
<td>total levodopa equivalent drug dose*</td>
<td>1255 ± 509</td>
</tr>
<tr>
<td>median follow up in mos (range)</td>
<td>24 (12–52)</td>
</tr>
<tr>
<td>no. of patients w/ &gt;2 yrs follow up (%)</td>
<td>11 (44)</td>
</tr>
<tr>
<td>no. of patients w/ &gt;3 yrs follow up (%)</td>
<td>9 (36)</td>
</tr>
</tbody>
</table>

* Mean ± standard deviation.

Statistical Analysis

Pairwise comparisons were made among baseline (preoperative) scores, scores at 1 year, and scores at the last evaluation by using the Wilcoxon signed-rank test. The mean total levodopa equivalents before and after surgery were compared using a paired Student t-test. Percentage changes in scores over time and 95% CIs were also calculated. The proportions of patients who experienced morning dystonia and painful dyskinesia at baseline and postoperatively were compared using the McNemar test.

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For those variables continuing to show a significant improvement at the last assessment, a repeated measures analysis of variance was performed to assess for a deterioration in function or an increase in drug dosage over time within individuals. We attempted to identify subgroups of patients among whom DBS of the STN was particularly beneficial or particularly lacking in efficacy. For these analyses the study cohort was stratified according to the age of the patient, characteristics of the disease (for example, tremor-predominant or axial-predominant symptoms), drug requirements prior to surgery, the presence of preoperative dyskinesia, and the patient’s preoperative response to levodopa. The median value for each of these categories was determined and the patients were divided into those in whom age, scores, and drug requirements and responses were greater or less than the median. Differences between the strata in changes of total UPDRS scores and of UPDRS motor and ADL subscores were evaluated using the Wilcoxon rank-sum test. All analyses were performed using a commercially available computer software program (Intercooled Stata, version 7.0; Stata Corp., College Station, TX).

**Results**

The baseline characteristics of the cohort are shown in Table 1. The mean age of patients at surgery was 57.2 years (range 34–76 years) and the mean duration of PD before surgery was 13.4 ± 4.3 years. The median follow-up time was 24 months (range 12–52 months); in nine patients 3 or more years of follow up were available.

**Results at 1 Year**

Changes in the UPDRS motor subscores under all conditions (stimulator off/medication off, stimulator on/medication off, stimulator off/medication on, and stimulator on/medication on) at baseline, 1 year postoperatively, and the last evaluation are depicted in Fig. 1. A significant improvement was seen in motor function and ADL subscores in the medication-off/stimulation-on period 1 year after surgery (Table 2). The mean improvement in the combined UPDRS scores was 42% relative to baseline (95% CI 35–49%, p < 0.001). The mean improvement in motor function scores was 48% (95% CI 42–55%, p < 0.001), whereas the ADL scores improved by a mean of 28% (95% CI 13–43%, p < 0.05). Improvements in dyskinesia scores during both medication-on and -off (generally dystonia during the medication-off time) periods were present 1 year after surgery; these improvements were significant compared with baseline values. The mean decrease in medication requirements at 1 year postoperatively was 38% (95% CI 25–50%, p < 0.001).

**Results at the Last Evaluation**

Significant improvements in the combined UPDRS scores and in the motor function and ADL subscores during the stimulation-on/medication-off period persisted at the time of the patient’s last follow-up examination (Table 2). Combined UPDRS scores were improved by a mean of 36% (95% CI 27–46%, p < 0.001). The mean improvement in motor function scores was 41% (95% CI 31–50%, p < 0.001), and the mean improvement in ADL scores was 24% (95% CI 7–41%, p < 0.001). The improvement in axial scores, relative to baseline, persisted, but the improvement in the PIGD score was not statistically significant. Axial scores remained significantly improved during the medication-on period compared with the medication-off period.

### Table 2: Comparison of Patient UPDRS Scores and Drug Dosages at Baseline, at 1 Year after Surgery, and at the Time of the Last Evaluation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Medication-Off / Stimulation-On Period</th>
<th>Medication-On / Stimulation-On Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 Yr</td>
</tr>
<tr>
<td>overall UPDRS score</td>
<td>76.6 ± 15.5</td>
<td>41.7 ± 10.6</td>
</tr>
<tr>
<td>motor score</td>
<td>50.1 ± 12.3</td>
<td>24.6 ± 7.3‡</td>
</tr>
<tr>
<td>ADL score</td>
<td>25.8 ± 5.7</td>
<td>17.4 ± 6.1‡</td>
</tr>
<tr>
<td>motor subareas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tremor</td>
<td>9.8 ± 5.9</td>
<td>1.5 ± 1.9‡</td>
</tr>
<tr>
<td>rigidity</td>
<td>9.2 ± 3.2</td>
<td>5.3 ± 2.5‡</td>
</tr>
<tr>
<td>bradykinesia</td>
<td>16.4 ± 4.3</td>
<td>9.8 ± 3.8‡</td>
</tr>
<tr>
<td>dyskinesia rating</td>
<td>1.6 ± 2.7</td>
<td>0.5 ± 0.6</td>
</tr>
<tr>
<td>disability (UPDRS IV)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>duration</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>% of day w/o medication</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>axial scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIGD</td>
<td>9.4 ± 4.1</td>
<td>4.2 ± 2.4‡</td>
</tr>
<tr>
<td>ADL</td>
<td>9.0 ± 3.4</td>
<td>6.8 ± 3.0§</td>
</tr>
<tr>
<td>drug dosage</td>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

* Scores are presented as the means ± standard deviations. Lower scores indicate better function. Baseline scores were assessed before surgery; 1-year scores cover those from evaluations performed between 8 and 15 months after surgery; last evaluation denotes the last examination obtained in patients. Last evaluations were performed a mean of 30 months after surgery (range 12–52 months). Explanation of UPDRS categories can be found in Clinical Material and Methods. Abbreviation: NA = not applicable.
† Probability values were determined by pair-wise comparisons of the baseline score with scores obtained at the last evaluation by using the Wilcoxon signed-rank test.
‡ p < 0.001 compared with baseline score.
§ p < 0.05 compared with baseline score.
|| Drug dosage is presented in levodopa equivalents and is calculated according to a standardized formula. Probability values associated with changes in drug dosage were calculated using paired Student t-tests.
period at the last evaluation. Nevertheless, the patients’ response to medication, as reflected by the PIGD score, was better at baseline (decrease of 49.9%, 95% CI 37–62%, \(p < 0.001\)) compared with the response to medication at the last evaluation (decrease of 32.7%, 95% CI 19.3–41.2%, \(p < 0.001\)). This was also true of the ADL axial scores (data not shown). Dyskinesia, disability, and duration scores during the medication-on period remained significantly improved relative to baseline. There was a significant difference in morning dystonia before surgery compared with the last evaluation (\(p = 0.07\)). Six patients had morning dystonia at the last evaluation compared with 12 preoperatively. There was also a significant reduction in the duration of the medication-off time. Medication dosage remained substantially diminished from baseline, with a mean reduction of 36% (95% CI 22–50%, \(p < 0.001\)).

When analyses were restricted to the nine individuals in whom 3 or more years of follow-up data were available, the mean improvement in motor function scores during the medication-off period was 35% (95% CI 18–53%, \(p = 0.022\)) and the mean improvement in the ADL scores was 22% (95% CI 9–36%, \(p = 0.039\)).

### Changes in Function Over Time

When postoperative stimulation-on UPDRS scores were evaluated using repeated-measures analysis of variance, there was significant worsening in the combined UPDRS scores during the medication-off period within individuals over time (\(p = 0.012\)), although the scores remained significantly improved compared with baseline values, as noted earlier. The UPDRS motor subscores also worsened significantly over time (\(p = 0.018\)), whereas the ADL subscores did not change significantly (\(p = 0.19\)). With regard to axial scores, axial ADL scores did not deteriorate significantly over time (\(p = 0.37\)), but PIGD scores did (\(p = 0.005\)). There was no evidence of worsening of dyskinesia scores during the medication-on (\(p = 0.83\)) and -off periods. There was no significant increase in medication requirements (\(p = 0.74\)) over time.

No significant differences were found for total motor scores or for individual rigidity, bradykinesia, tremor, and axial subscores when preoperative scores were compared with scores obtained at the last evaluation during the medication-off/stimulator-off state.
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Stratified Analysis

Stratified analyses were performed to evaluate the possibility that subgroups of patients might differ with regard to long-term outcomes after surgery (Table 3). Nevertheless, no significant differences in combined UPDRS scores, motor function subscores, or ADL subscores were detected when the study cohort was stratified according to patient age, sex, preoperative disease duration, baseline drug dosage requirements, preoperative dyskinesia, or patient age at onset of PD. The only variable predictive of a sustained response to surgery, as measured by the UPDRS motor response, was the preoperative response to levodopa (p = 0.004).

Individuals with a more marked tremor at baseline, defined as a baseline UPDRS tremor subscore that was higher than the cohort median, had a significantly greater change in the UPDRS motor subscore 1 year after surgery than did individuals with less prominent tremor (p = 0.002). No difference, however, was observed between individuals with prominent tremor and those with less prominent tremor or with regard to a postoperative improvement in the combined UPDRS scores or the ADL subscores. No difference in outcome was seen in individuals with prominent rigidity, bradykinesia, or axial scores when compared with individuals in whom these features were less prominent.

Adverse Events

Most patients experienced transient parasthesia, diplopia, or muscle twitches during the normal adjustment period in which the best parameters were selected to maximize benefit and minimize adverse events during programming. Serious adverse events are listed in Table 4. There was no occurrence of intracranial hemorrhage and no report of intraoperative complications in this group of patients. The most common adverse effects of surgery were difficulty with speech in six patients and cognitive impairment in five patients. Four patients experienced some mood changes and one of these attempted suicide. Three individuals had delayed wound healing and cellulitis developed in the scalp overlying the electrode wires; these individuals received antibiotic medications and had successful resolution of the infection. In two of these patients the infection occurred within 8 weeks after surgery and in the third patient cellulitis occurred 9 months postoperatively. The fourth patient had scalp erosion due to the electrode and cellulitis; this patient ultimately required a skin graft at the electrode site. The infection in this individual occurred within 2 months after surgery.

Discussion

We evaluated the effects of DBS of the STN in a cohort of patients with advanced PD who were followed up for 1 or more years after surgery. We found that bilateral DBS of the STN resulted in a significant reduction in the combined UPDRS scores, as well as in the motor function and ADL subscores during the medication-off state. This effect was prominent 1 year after surgery and, although improvements in the combined UPDRS scores and motor function subscores declined significantly over time, these scores were still improved at the time of the last evaluation compared with baseline scores. Indeed, these benefits to motor function and ADLs were still present 3 or more years after the procedure.

Although it is difficult to compare the relative magnitude of a response among different components of the motor function subscore, we noted marked improvements in patients’ tremor scores at 1 year postoperatively, which were similar at the final evaluation. Indeed, patients with higher initial tremor scores had particularly marked improvements in motor function following surgery; this was likely due to the successful amelioration of the tremor. Although less dramatic, we also noted significant improvements in bradykinesia and rigidity, which were sustained over time. Axial symptoms (reflected by PIGD scores), which may be more resistant to dopaminergic therapy, did improve initially; however, these improvements were no longer significant at the time of the last evaluation. In contrast, PIGD and ADL axial scores significantly improved in response to medication at baseline, at 1 year postoperatively, and at the last evaluation, challenging the notion that the effectiveness of DBS of the STN on axial symptoms can be completely predicted by the response to the best medication-on response presurgically. In an analysis of predictive factors that influence outcome of STN stimulation, Welter, et al., relied on data obtained during a 6-month follow-up period and did not obtain long-term data. Of note, in our analysis of the patients’ response to medication compared with their response to DBS of the STN, there was no statistically significant difference in motor subscores (tremor, rigidity, and bradykinesia) at each postoperative evaluation, implying that DBS does not provide a greater benefit than medication.

Other studies designed to evaluate individuals longer than 1 year after implantation of a DBS device in the STN have found no loss of benefit from DBS over time. Failure to find such an effect may be due to the inadequate...
statistical power of these studies, several of which contained cohorts that were smaller than the one presented here. It might be argued that the diminution over time in the effect of DBS of the STN on motor symptoms reflects progression of the underlying disease, rather than a loss of efficacy. Nevertheless, consistent with other studies, we found no significant difference between UPDRS motor function subscores assessed for the medication-off period at baseline and those obtained at the last evaluation with the DBS device turned off. This might suggest that the underlying disease did not progress greatly during the period of study; however, the analysis of the medication-off/stimulation-off scores may not be a good measure of the progression of underlying disease. Initially, scores obtained during the stimulation-off period would indicate a microsubthalamotomy effect and, later, scores could be influenced by an effect of long-term stimulation, which is not lost following a short-term withdrawal of stimulation (for example, neuroplasticity) and, possibly, even a cumulative lesion effect. Furthermore, in patients with late-stage PD, progression of disease may be considerably slower than during earlier stages. It is also possible that the scale sensitivity to rate changes in late-stage PD is poor. Finally, it is clear that overnight withdrawal of medication does not accurately represent the true untreated disease state. As such, it may be difficult to assess underlying disease progression adequately in patients who have undergone STN stimulation.

It is notable that, although statistically significant, the decreases in the effect of DBS of the STN on motor function over time was of small magnitude, but was not sufficient to cause the treating clinicians to increase patients’ antiparkinsonian medication dosage. Medication dosage decreased sharply during the 1st year after surgery, and remained reduced over time; this was probably a major contributing factor to the marked reduction in dyskinesia that we observed during evaluations conducted in patients in the medication-off period. It is possible, however, that there is an additional ameliorative effect of long-term DBS of the STN on dyskinesias that is independent of drug dosage because a reduction in dyskinesia could be seen in patients in whom no drug reduction was reported following DBS. Dyskinesias are frequently a source of distress to patients with PD, and the sustained nature of this improvement suggests that DBS of the STN may have a marked impact on the patient’s health-related quality of life as experienced both during the medication-off and -on periods.

The magnitude of improvement in UPDRS motor function subscores observed in our cohort is similar to those associated with other published series. The reduction in medication dosage is comparable to that described in the largest series published to date, although it is less than the 50 to 80% reduction reported in some series. The reduction in dyskinesia scores was also comparable to results obtained in a recent large multiinstitutional report, but less dramatic than reductions of up to 90% reported elsewhere. These differences may reflect our relatively conservative approach to withdrawal of medications, which may result in fewer adverse experiences, particularly related to speech and behavior.

Despite the relative safety of this procedure, we noted a number of transient and sustained adverse effects of surgery in this cohort. Our observation that impairment of speech occurs commonly after surgery is consistent with the findings of other studies. Although it is true that most patients have features of hypophonia or dysarthria preoperatively as a symptom of their parkinsonism, some of our patients reported equivocal worsening after surgery and over time displayed progression of speech difficulties that were not modifiable by adjusting the stimulator or medications. Psychological problems and cognitive deterioration were also relatively common in this series, especially in older patients; these affected memory, verbal fluency, and executive function. Only patients who complained of cognitive problems underwent formal neuropsychological testing; many of these patients have been included in our earlier report of the results of formal neuropsychological testing in patients who have undergone DBS of the STN. This is also in keeping with other reports on cognitive outcomes of patients undergoing STN stimulation.

Three of our patients had depression several months after surgery, in all cases this was controlled with antidepressant medications. One other patient attempted suicide although he did not have other symptoms of depression and did not require treatment. His suicide attempt was interpreted as an impulsive act that was related to a specific circumstance. The causes for depression in these patients may be multifactorial: related to surgery, stimulation, or reduction of medications, or stemming from social adjustment issues associated with their new status of being well rather than an invalid. Some patients may also have denied premorbid psychiatric conditions to increase their likelihood of surgery. Despite the fact that psychiatric illness was an exclusion criterion, patients who otherwise would not have been considered surgical candidates may have received surgery. A retrospective analysis of 24 patients who were successfully treated by DBS of the STN found that surgery commonly resulted in worsening of prior psychiatric conditions. This compilation of adverse events serves to underscore the fact that patients with preoperative cognitive deficits, psychiatric symptoms, or speech difficulties are at risk for worsening of these problems as a result of surgery. Careful patient selection with attention to these factors is important to maximize the benefit and limit the adverse effects of this treatment. Despite the occurrence of adverse events in some of our patients, all reported that the benefit of surgery outweighed any problems that they experienced following the surgery.

**Conclusions**

In this group of patients who underwent DBS of the STN for intractable symptoms of PD, there was a sustained long-term amelioration of symptoms with reduction in motor disabilities, medication requirements, and dyskinesias. Although our results confirm the relative safety and efficacy of this procedure in a selected group of patients, significant adverse events did occur, underlining the fact that the potential benefits of this surgery need to be carefully weighed against its risks. Nonetheless, our results suggest that DBS of the STN can be a very valuable therapeutic tool in selected patients with advanced PD.

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References


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