

# Deep Brain Stimulation of the Subthalamic Nucleus in Parkinson's Disease

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## ABSTRACT

**Objective:** To evaluate the clinical effects of subthalamic nucleus deep brain stimulation in patients with Parkinson's disease within the first 12 months after surgery.

**Methods:** We performed a prospective study in 8 patients with Parkinson's disease, in whom electrodes were implanted in the subthalamic nucleus bilaterally. We compared levodopa-equivalents and the scores of the Unified Parkinson's Disease Rating Scale pre- and post-operatively. The post-operative evaluation was done between 3 and 12 months after surgery.

**Results:** Antiparkinsonian medications were reduced post-operatively by a mean of 61.5% ( $P < 0.01$ ) from a levodopa-equivalent dosage of  $1144.9 \pm 572.5$  mg/day to  $440.9 \pm 172.1$  mg/day. Motor scores improved 44.4% ( $P < 0.01$ ) and activities of daily living scores 38.2% ( $P < 0.01$ ). Adverse events included a subcutaneous hematoma in 1 patient after internal pulse generator implantation necessitating evacuation.

**Conclusions:** Bilateral stimulation of the subthalamic nucleus is associated with significant improvement in motor function and reduction of antiparkinsonian medications in patients with Parkinson's disease in the first 12 months after surgery. On-state dyskinesias were greatly

reduced, probably due to the reduction of total antiparkinsonian medications. The procedure is well tolerated.

## INTRODUCTION

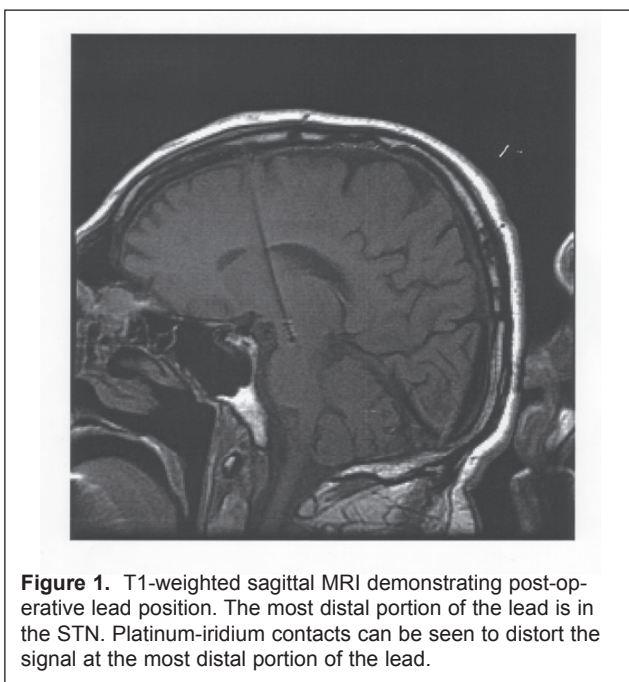
It has been shown that the subthalamic nucleus (STN) is hyperactive in the parkinsonian state and that a direct lesion or functional inactivation of the STN relieves parkinsonian features in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys.<sup>1</sup> It is also well established that anatomic lesions of the STN can result in hemiballism. Consequently, stereotactic neurostimulation may provide a suitable method for treating symptoms of Parkinson's disease (PD) without producing a permanent lesion. Among neurologic disorders, PD is a prototypic example of a condition in which neurochemical, electrophysiological, and anatomical knowledge has led directly to clinical advances. Although current pharmacologic treatment is effective based on the use of multiple agents, it has limitations.<sup>2</sup> Most of the patients treated with levodopa or other antiparkinsonian medications for more than 5 years suffer from motor fluctuations and psychiatric side effects.<sup>3</sup> Several studies have demonstrated consistent benefit from unilateral pallidotomy with respect to contralateral levodopa induced dyskinesias.<sup>4,5</sup> However, these irreversible lesions are associated with the risk of permanent neurological deficits, and any alteration of the size or location of the lesion requires additional intracranial surgery.<sup>3</sup> Deep brain stimulation (DBS) provides an alternative to lesioning that may not be accompanied by the same risk of permanent complications. Furthermore, bilateral procedures are available. Subthalamic nucleus deep brain stimulation (STN-DBS) is an effective treatment for properly selected patients.<sup>6</sup> STN-DBS improves the cardinal symptoms of PD such as tremor, rigidity, bradykinesia/akinesia, and postural instability, and reduces motor fluctuations. Also, it is the only surgical treatment that allows levodopa dose reduction. Advances in surgical techniques, neuroimaging, and electrophysiological recordings allow stereotaxic procedures to be done more

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**Table 1.** Baseline Characteristics of Subjects

Cases Age/Sex	Duration of PD (Years)	Levodopa Equivalents (mg/day)	UPDRS with Medication
(1) 51M	6	960	30
(2) 75F	6	600	53
(3) 65M	8	1514	41
(4) 55M	17	1620	61
(5) 63M	18	520	64
(6) 60M	10	2175	59
(7) 63M	22	970	51
(8) 54F	19	800	35
60.1±7.6	13.3±6.4	1144.9±572.5	49.3±12

Values are means ± standard deviations (SD). UPDRS= Unified Parkinson's Disease Rating Scale



**Figure 1.** T1-weighted sagittal MRI demonstrating post-operative lead position. The most distal portion of the lead is in the STN. Platinum-iridium contacts can be seen to distort the signal at the most distal portion of the lead.

accurately and safely. Although the short-term benefits of bilateral STN-DBS in PD patients have been documented in multi-center studies,<sup>5</sup> we investigate the effectiveness of this treatment in the first 12 months after surgery by a prospective study at the University of Wisconsin (UW)-Madison Functional Neurosurgery Program.

**METHODS**

*Patients*

Eight patients who underwent surgery to implant electrodes in the STN bilaterally were enrolled in this study. All patients were diagnosed with idiopathic PD and continued to suffer from motor symptoms of PD despite adequate medical therapy. They were evaluated in the Functional Neurosurgery Clinic where the recom-

mendations for STN-DBS were based on: (1) diagnosis of idiopathic PD; (2) beneficial response to levodopa; (3) persistent symptoms despite medical management; and (4) no surgical contraindications. Exclusion criteria included those with dementia or active psychiatric symptoms. This study was approved by the UW-Madison Human Subjects Committee and all subjects signed an informed, written consent form. Baseline characteristics are shown in Table 1.

*Surgical Procedure*

Stereotactic surgery was performed in the practically defined “off” condition (no levodopa administration for at least 10 hours). Each patient received bilateral STN implants during a single surgical procedure. A Cosman-Roberts-Wells (Radionics, Inc., Burlington, MA) stereotactic head frame was placed on the patient under local anesthesia.

Stereotactic coordinates for each patient were determined using magnetic resonance imaging (MRI) to localize the anterior commissure (AC) and posterior commissure (PC). The STN was then localized using standard measurements from the anatomical atlas of Schaltenbrand and Baily.<sup>7</sup> The anatomical coordinates of the STN were 3 mm posterior to the midcommisural point, 4 mm inferior and 12 mm lateral to the AC-PC line. Microelectrode recording was used to refine the exact location of the STN in each patient. Recording was continued until the substantia nigra pars reticulata (SNr) was encountered. Each cell or cell group was assessed for change in firing frequency by voluntary and passive upper and lower extremity movements. Microelectrode recording was followed by intraoperative electrical stimulation to confirm the presence of beneficial effects such as suppression of tremor, rigidity, and the absence of side effects such as diplopia, persistent paresthesias, and muscle contractions. Once the final target was determined, the microelectrode was removed and replaced by the permanent stimulating quadripolar lead (Activa, DBS lead 3389, Medtronic, Inc., Minneapolis, MN). At a separate time the electrode was connected to an internal pulse generator (IPG; Soletra, model 7426, Medtronic Inc.) placed subcutaneously in the subclavicular region. Implantation of the IPG was performed under general anesthesia (Figure 1).

*Clinical Evaluation*

STN stimulation was continuous 24 hours per day. Patients were on the most effective dose of antiparkinsonian medications when they were evaluated pre- and post-operatively. Patients were evaluated on medications using the Unified Parkinson's Disease Rating Scale

(UPDRS),<sup>8</sup> which incorporates assessments of motor function, activities of daily living (ADL), and dyskinesia. Evaluations took place both pre- (<3 months) and 3-12 months post-operatively. The evaluations for tremor, rigidity, and bradykinesia were done on the most severely affected extremity. Subsequently, the range of the scores were tremor 0-8, rigidity 0-4, and bradykinesia 0-8.

Levodopa-equivalent doses were also calculated and reported for each patient both pre- and post-operatively. Levodopa-equivalent doses were calculated as follows: 100mg of standard levodopa=125mg of controlled-release levodopa=10mg of bromocriptine=1 mg of pergolide=1mg of pramipexole=3 mg of ropinirole. Any other medications such as selegiline, amantadine, entacapone, tolcapone, and anticholinergic agents were not included in this evaluation.<sup>9</sup> Evaluations were completed in the patients' presenting state. An unblinded member of the research team, who was not part of the surgical team, administered the UPDRS at the patients' pre- and post-operative appointments.

*Statistical Analysis*

Data are presented as means, plus-minus standard deviation (SD). Mean values for parametric measures were compared using Student's t-tests, and mean values for nonparametric measures were analyzed by Wilcoxon signed rank test. All P values were 2-tailed, and less than 0.05 was considered statistically significant.

**RESULTS**

At the time of implantation, the patients were 60.8±7.6 years old (range 51-75 years). There were 6 men and 2 women and had a mean disease duration of 13.3±6.4 years (range 6-22 years). Table 2 summarizes the results of this study. Antiparkinsonian medications were reduced post-operatively by a mean of 61.5% (P<.01) from a levodopa-equivalent dosage of 1144.9±572.5 mg/day to 440.9±172.1 mg/day. Motor scores improved 44.4% (P<.01) and ADL scores 38.2% (P<.01). Tremor, rigidity, and bradykinesias were all improved. A positive effect on postural instability and gait disturbance was also apparent. Motor fluctuations improved in all patients. Dyskinesias were reduced dramatically, most likely due to the marked reduction of levodopa dosage. Dyskinesia scores improved 81.2% (P<.01) and "off" periods 60.0% (P<.01). The off dystonia was alleviated synchronously with stimulation. The "on" period dyskinesias were reduced in parallel with significant reduction of the levodopa-equivalents. Mentation improved significantly.

All patients were stimulated using monopolar settings. Transient adverse effects such as contralateral paresthesias and tonic contractions, dysarthria, diplopia,

**Table 2.** Baseline and Post-Operative Scores in Subjects With Bilateral STN-DBS

Parameters	Baseline	Post-Operation	Change	P Value
Levodopa-equivalents	1144.9±572.5	440.9±172.1	-61.5%	0.0018
<b>UPDRS subscores</b>				
Mentation	4.8±3.1	2.1±2.2	-56.3%	0.0152
ADL	17.0±5.7	10.5±6.3	-38.2%	0.0031
Total Motor score	18.0±5.5	10.0±5.5	-44.4%	0.0036
Tremor	3.3±2.3	1.1±1.9	-66.7%	0.0005
Rigidity	1.6±0.9	0.1±0.4	-93.8%	0.0025
Bradykinesia	5.5±1.9	2.6±1.5	-52.7%	0.0043
Gait	1.8±1.2	0.6±0.9	-66.7%	0.0256
Postural instability	1.3±1.4	0.6±0.9	-53.8%	0.0491
Dyskinesias	2.0±1.2	0.4±0.7	-80.0%	0.0096
"Off" periods	2.0±0.4	1.0±0.7	-50.0%	0.0066
<b>Total UPDRS scores</b>	<b>49.3±12.6</b>	<b>26.1±15.6</b>	<b>-47.1%</b>	<b>0.0002</b>

All values are means ±SD.  
 STN-DBS=Subthalamic nucleus deep brain stimulation; UPDRS=Unified Parkinson's Disease Rating Scale; ADL=Activities of daily living

and blurred vision occurred in all patients as the optimal stimulation adjustments were being sought. These adverse effects were transient at the initial stimulation, or subsided immediately when the stimulation parameters were altered. Severe surgical complications, such as intracerebral hemorrhage, were not observed. One patient (case 6) had hematoma in the subcutaneous pocket for the IPG, which required evacuation.

**DISCUSSION**

This study shows that bilateral STN-DBS improved all motor features of PD that responded to levodopa pre-operatively. The results of this study are comparable with results from other studies with an improvement in UPDRS scores.<sup>2,3,5,6,10</sup> Tremor and rigidity improved substantially within 12 months. Bradykinesia also improved within 12 months, but not completely. The duration of dyskinesia and the severity of dyskinesia associated disability substantially decreased within 12 months.

DBS is a relatively new surgical option for patients with PD who continue to have symptoms despite medical treatment. The advantage of DBS over more traditional surgical interventions (e.g., pallidotomy and thalamotomy) is a lower risk of complications and the ability to adjust the size of the "lesion" after surgery. While the exact mechanism of action of DBS is still under investigation, it has, to date, mimicked a lesion. Another advantage is that since only minimal tissue damage occurs, the device can be turned off with the patients returning

to their pre-surgical state. STN-DBS is the only known treatment for PD that allows a marked reduction in the dose of dopaminergic medications.

The disadvantage of DBS is cost, although it is approved by the Food and Drug Administration and Centers for Medicare and Medicaid Services. The system runs on a battery typically lasting 5 years. Replacement of the battery is usually an outpatient procedure where only the subclavicular incision is opened, and the intracranial lead is unaltered. The risk of infection is similar to other procedures, however, once an infection is diagnosed, antibiotics and explanation are often required for the definitive treatment. STN-DBS requires close follow-up of the patient, (ie, frequent therapeutic adjustments are essential for the patient until a good balance is achieved between the amount of stimulation and dopaminergic medications).

An increasing number of reports on psychiatric and behavioral adverse effects of STN-DBS has raised concerns about the safety of this therapy and deserves special attention.<sup>11</sup> PD is a neuropsychiatric disease most frequently associated with depression and anxiety. Mood and behavioral abnormalities post-operation often reflect a preexisting psychiatric condition. We had 1 case suffering from PD for 22 years who did not show improvement of UPDRS subset I; mentation, behavior and mood post-operatively. The case implies the longer the patients have PD, the more difficult to achieve the post-operative improvement for subset I. It is important to note, however, that in most patients, psychiatric disturbances are mild and transient.<sup>11</sup> Baseline neuropsychological studies on all patients are recommended pre-operatively.

The UW Functional Neurosurgery team has successfully initiated a DBS program with results consistent with larger multi-centric trials.<sup>5</sup> Patients were found to report an overall stability of symptoms in their "on" state, less time spent in the "off" state, and less time experiencing dyskinesia. Past studies have found that the most significant benefits are reported in the change in the patient's "off" state, less significant changes being reported in the "on" state.<sup>5</sup> It therefore could be expected that even more drastic changes could have been observed in UPDRS scores if patients were evaluated both pre- and post-operatively in the "off" state.

## CONCLUSIONS

Bilateral STN-DBS is an effective and safe treatment for the selected patient with PD who can no longer be improved by adjustment of antiparkinsonian medications. It makes significant reductions in the levodopa-equivalents, and significant improvement in UPDRS motor

scores and ADL scores within 12 months post-operatively. The most significant result of deep brain stimulations of the subthalamic nucleus is that it leads to a substantial reduction in motor fluctuations and dyskinesias. This study implies that STN-DBS might be superior to pallidal stimulation for treating PD, but further studies and follow-up are required.

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