One-year Outcome of Bilateral Subthalamic Stimulation in Parkinson Disease: An Eastern Experience

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BACKGROUND: **Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is widely accepted as a treatment for advanced Parkinson disease (PD). However, published studies were conducted mainly in Western centers and recruited small numbers of patients. This study presents 1-year outcomes in Taiwanese patients with PD.**

METHODS: **Sixty-two consecutive patients underwent STN-DBS surgery during a 7-year period. Their median drug-off Hoehn and Yahr stage was 3 and mean illness history was 8 years. Clinical outcomes were evaluated by the change in drug-off/DBS-on Unified Parkinson Disease Rating Scale (UPDRS) scores relative to presurgical drug-off baseline and change in daily levodopa-equivalent dose (LED).**

RESULTS: **After 1 year of DBS therapy, patients showed significant improvements with a clinically high effect size in cardinal signs, particularly in tremor (63%). Posture instability was also improved, whereas speech dysfunction was hardly corrected. The LED need was significantly reduced, therefore preoperative drug-induced complications were prominently (51%) ameliorated after surgery and drug-induced dyskinesia was remarkably (63%) diminished. No serious adverse effects were encountered after surgery. Overall, motor functions declined by 15% within 1 year in drug-off state.**

CONCLUSIONS: **Bilateral STN-DBS therapy provided effective and sustained benefits to Eastern patients with PD over a 1-year period.**

INTRODUCTION

Parkinson disease (PD) is a progressive neurodegenerative disorder characterized by motor and nonmotor symptoms (8, 11). Medication is the mainstay of treatment (6). Long-term dopaminergic therapy is limited by disease progression and development of motor fluctuations and dyskinesia (5, 6). Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is increasingly being accepted as an adjunct therapy for these patients (2, 6). Published reports demonstrated that clinical improvements after STN-DBS therapy alone varied widely from 20% to 80% in the first postoperative year compared with preoperative drug-off baseline (1, 9, 13, 14, 17-19). However, most of these studies recruited only a small number (median, 25) of patients and were conducted in Western centers (9, 13). A PubMed search of the English literature up to December 2014 yielded only 1 Japanese study (8 patients) reporting 1-year outcomes (12). To address the gap in demonstrated STN-DBS efficacy between Western and Eastern patients with PD, we present our surgical results in 62 patients over a 7-year period.

MATERIALS AND METHODS

Patients

Sixty-two consecutive patients (43 men, 19 women) underwent bilateral STN-DBS therapy up to October 2013. Movement disorder specialists screened the surgical candidates according to the CAPSIT-PD (core assessment program for surgical interventional therapies in Parkinson's disease) criteria (4). Patients with substantial cognitive dysfunction as indicated by a Mini-Mental State Examination score $\leq$20, major depressive disorder, or severe concomitant medical comorbidities were excluded. The mean age in this series was 61 years and the mean duration of illness was

Key words
- Deep brain stimulation
- Effect size
- Levodopa
- Parkinson disease
- Prognosis
- Subthalamic nucleus

Abbreviations and Acronyms
η^2: Effect size
ADL: Activities of daily living
DBS: Deep brain stimulation
LED: Levodopa-equivalent dose
LD: Levodopa
PD: Parkinson disease
PIGD: Postural instability and gait disturbance
STN: Subthalamic nucleus
UPDRS: Unified Parkinson Disease Rating Scale

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8 years. Median drug-off Hoehn and Yahr stage was 3 (Table 1). The preoperative mean levodopa (LD) response was a 33% reduction in the Unified Parkinson Disease Rating Scale (UPDRS) Part III (motor) subscore. The mean greatest motor improvement after the LD challenge test was 48%. This study complied with all institutional guidelines and regulations of the Declaration of Helsinki. Before surgery, all patients provided written informed consent approved by the local ethic committee.

Surgical Technique and Programming

All patients underwent a 2-stage standardized operation by the same neurosurgeon (C.S.M.). In brief, dopaminergic medication was stopped overnight for at least 12 hours before surgery. Intravenous antibiotics were routinely administered before surgery plus 7 days on oral antibiotics after the procedure as prophylactic therapy. In the first session, bilateral STN electrodes (model 3389, Medtronic, Minneapolis, Minnesota, USA) were implanted under local anesthesia using a standard stereotaxic technique. STN was targeted using T2-weighted magnetic resonance images and intraoperative electrophysiologic guidance.

We used single-track microelectrode recordings to identify the somatosensory region of the STN and its boundary to the substantia nigra, based on their characteristic neuronal firing patterns and responses to passive movements of the contralateral limbs. The length of the trajectory should be at least 4.0 mm, otherwise another entry should be tried. A total of 157 passes were performed with an average of 1.3 ± 0.1 passes per lead implantation. The final mean lateral (x), anteroposterior (y), and vertical (z) coordinates were 11.8 ± 0.2, −3.4 ± 0.2, and −4.6 ± 0.2 mm relative to the mid-commissural point, respectively. The implantable pulse generator (IPG) (Kinetra) was placed under general anesthesia 5 days later.

Table 1. Baseline Demographic Characteristics of Patients Before Surgery

Men:Women	43:19
Age at surgery (years)	60.8 ± 2.4 (40–78)
Duration of illness at surgery (years)	8.2 ± 0.8 (5–17)
Median Hoehn and Yahr (off) stage	3 (2–5)
Mini-Mental State Examination score	27.1 ± 0.7 (21–30)
Levodopa-equivalent daily dose (mg)	671.8 ± 95.3 (50–1867)
Improvement after levodopa challenge test (%)	47.7 ± 3.8
Preoperative drug-off UPDRS total score	67.7 ± 5.9 (24–149)
Preoperative drug-on UPDRS total score	48.1 ± 5.1 (8–92)
Preoperative drug-off UPDRS part II score	19.0 ± 2.0 (3–45)
Preoperative drug-on UPDRS part II score	12.8 ± 1.7 (1–32)
Preoperative drug-off UPDRS part III score	40.5 ± 4.0 (10–90)
Preoperative drug-on UPDRS part III score	27.1 ± 3.6 (4–64)

Values are means ± 95% confidence interval (range).
UPDRS, Unified Parkinson Disease Rating Scale.

Programming was initiated 2–3 weeks after IPG implantation when the lesion effects had faded. After optimizing the settings, the stimulator was left on continuously. One year after surgery, the mean parameters for the right stimulator were 2.8 ± 0.2 V amplitude; 65.4 ± 3.0 milliseconds pulse width; and 140.0 ± 3.5 Hz frequency. For the left stimulator, the parameters were 2.9 ± 0.1 V, 65.8 ± 3.0 milliseconds, and 140.0 ± 3.5 Hz, respectively. Monopolar stimulation was used in 73% (n = 45) of the patients. Another 2 patients were treated using a bipolar/monopolar combination.

Clinical Assessments

Clinical follow-up visits were scheduled every 2 weeks during the first 3 months after surgery and at 3-month intervals thereafter. Patients were assessed after at least 12 hours overnight withdrawal of anti-parkinsonian medication, first in the DBS-on state; and repeatedly at least 30 minutes after the start of the DBS-off state. The primary end point was the change in drug-off UPDRS total score, part II (activities of daily living [ADL]) and motor subscores relative to the preoperative drug-off baseline. A higher score indicates a worse condition. Motor outcome measures were focused on speech (UPDRS item 18), tremor (items 20 and 21), rigidity (item 22), and akinesia (items 23–26). Locomotion dysfunction was expressed as postural instability and gait disturbance (items13–15, 29, and 30). Dyskinesia (items 32–35) was also calculated. The secondary end point was the reduction in daily LD-equivalent dose (LED).

Statistical Methods

Five patients (8%) missed the 1-year follow-up, thus a later follow-up was carried forward and treated as the 1-year follow-up. All the data were expressed as means and 95% confidence intervals. Continuous variables were examined for normality using the Kolmogorov-Smirnov test. Preoperative drug-off versus drug-on difference in UPDRS scores was compared using the Wilcoxon signed-rank test. The changes in UPDRS scores and daily LED over time were assessed using repeated measurements analysis of variance with within-factors of time events (6 months and 1 year relative to the preoperative drug-off baseline). The Mauchly test was performed to evaluate the sphericity assumption using the Huynh-Feldt correction for adjustment. Relevant differences in time events were evaluated using a post hoc Bonferroni test. Clinical significance was expressed as effect size (η^2) with cut-off points of low (0.01), moderate (0.06), and high (0.14) (10). All statistical analyses were performed using PASW Statistics 18 (SPSS Inc., Chicago, Illinois, USA). A 2-tailed P value less than 0.05 indicated statistical significance.

RESULTS

Overall Clinical Efficacy of DBS Therapy

After 1 year of STN-DBS therapy without medication, patients experienced clinical improvement with high effect size in the drug-off/DBS-on condition compared with the preoperative drug-off baseline (Table 2), as indicated by a 22% decrease in UPDRS total scores ($\eta^2 = 0.33$, $P < 0.001$), a 20% decrease in ADL ($\eta^2 = 0.24$, $P < 0.001$), and a 22% decrease in motor ($\eta^2 = 0.26$, $P < 0.001$) subscores. Comparing the postoperative