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ORIGINAL ARTICLE

Comparison of Pallidal and Subthalamic Deep Brain Stimulation in Parkinson's Disease: Therapeutic and Adverse Effects

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ABSTRACT

Objective To compare the therapeutic and adverse effects of globus pallidus interna (GPi) and subthalamic nucleus (STN) deep brain stimulation (DBS) for the treatment of advanced Parkinson's disease (PD).

Methods We retrospectively analyzed the clinical data of patients with PD who underwent GPi (n = 14) or STN (n = 28) DBS surgery between April 2002 and May 2014. The subjects were matched for age at surgery and disease duration. The Unified Parkinson's Disease Rating Scale (UPDRS) scores and levodopa equivalent dose (LED) at baseline and 12 months after surgery were used to assess the therapeutic effects of DBS. Adverse effects were also compared between the two groups.

Results At 12 months, the mean changes in the UPDRS total and part I–IV scores did not differ significantly between the two groups. However, the subscores for gait disturbance/postural instability and dyskinesia were significantly more improved after GPi DBS than those after STN DBS (p = 0.024 and 0.016, respectively). The LED was significantly more reduced in patients after STN DBS than that after GPi DBS (p = 0.004). Serious adverse effects did not differ between the two groups (p = 0.697).

Conclusion The patients with PD showed greater improvement in gait disturbance/postural instability and dyskinesia after GPi DBS compared with those after STN DBS, although the patients had a greater reduction in LED after STN DBS. These results may provide useful information for optimal target selection for DBS in PD.

Key Words Parkinson's disease; deep brain stimulation; globus pallidus interna; subthalamic nucleus.

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is characterized by resting tremor, bradykinesia, rigidity, and other motor and non-motor clinical features.[1,2] Patients with PD typically have a robust response to levodopa or dopamine agonist therapies. However, after 5 to 10 years of medical therapies, medication-related complications may occur in a majority of patients with PD. Patients who develop motor complications may not be adequately managed by medication adjustments and therefore become appropriate potential candidates for deep brain stimulation (DBS).[3]

DBS of the globus pallidus interna (GPi) or subthalamic nucleus (STN) is an accepted surgical treatment for advanced PD when motor symptoms can no longer be treated adequately with medications. Recent studies have reported that GPi and STN DBS are similarly effective in improving motor symptoms and quality of life for patients with PD over the course of 2–3 years.[4,5]

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However, it is still unclear whether there are definite advantages or disadvantages in selecting one target over another for DBS in patients with advanced PD. One target may improve a certain specific clinical symptom more effectively than another target; there may also be ethnic differences in the therapeutic effects of DBS. Moreover, the therapeutic effects and quality of life after DBS surgery may be influenced by post-operative medications that vary substantially among different countries (Supplementary Table 1 and 2 in the online-only Data Supplement). Therefore, the aim of this study was to provide a detailed comparison of the therapeutic and adverse effects of GPi versus STN DBS surgery.

MATERIALS & METHODS

Subjects

We retrospectively analyzed 147 patients with advanced PD who received bilateral GPi or STN DBS between April 2002 and May 2014 in the Departments of Neurology and Neurosurgery at Asan Medical Center, Seoul, Korea. All patients with PD underwent DBS surgery based on the institutional guideline for DBS surgery, including clinically diagnosed PD of > 5 years in duration; severe levodopa-induced motor complications despite optimal adjustment of anti-parkinsonian medications; no evidence of Parkinson-plus syndrome or secondary parkinsonism; no surgical contraindications; and no severe dementia, depression, or psychosis. In pre-surgery assessment, all patients showed an improvement in the Unified Parkinson's Disease Rating Scale (UPDRS) part III motor score of > 30% in the levodopa challenge test by taking a suprathreshold dose of levodopa [150% of the usual first morning levodopa equivalent dose (LED) based on the pre-surgery usual first morning dose of anti-parkinsonian medication] (Supplementary Table 3 in the online-only Data Supplement).

Fourteen patients with PD underwent bilateral GPi DBS surgery during the study period and were enrolled in this study. For comparisons, 28 patients with PD who received STN DBS surgery were selected by random assignment using a computer-generated randomization sequence, with matching for age at DBS surgery and disease duration of PD.

This study was approved by the Institutional Review Board of Asan Medical Center. The board waived the requirement for patient consent because of the retrospective and observational nature of the study.

Clinical assessment

All subjects underwent a systemic institutional clinical assessment that is described in detail in previous reports.[6-8] The patients were evaluated post-operatively at 3 months, 6 months, and annually. All patients were assessed for clinical symptoms using UPDRS under four conditions: 1) off stimulation–off medication, after stimulation had been switched off for 1 h; 2) on stimulation–off medication, after stimulation had been switched on for 1 h; 3) off stimulation–on medication, after stimulation had been switched off for 1 h and after the administration of a suprathreshold dose of standard levodopa; and 4) on stimulation–on medication. The specific subscores for bradykinesia (summation of UPDRS items 23–27 and 31), tremor (summation of UPDRS items 20 and 21), rigidity (UPDRS item 22), speech (UPDRS item 18), and gait disturbance/postural instability (UPDRS items 28–30) were assessed.[9] The subscores for dyskinesia (summation of UPDRS items 32–35) and motor fluctuation (summation of UPDRS items 36–39) were also assessed. The LED was calculated according to the following conversion formula: standard levodopa dose × 1 + slow - release levodopa × 0.75 + ropinirole × 20 + pramipexole × 100 + [standard levodopa + (slow - release levodopa × 0.75)] × 0.33 if taking entacapone.[10]

DBS surgical procedures

The GPi and STN DBS surgery procedures have been described in detail in previous reports.[6,7] The target sites (GPi or STN) for DBS were determined by a consensus decision made by physicians, patients, and their caregivers in clinical practice.

Statistical analysis

The baseline demographic and clinical data were analyzed using Student's *t*-test or Wilcoxon signed-rank tests. The UPDRS scores were analyzed using Mann-Whitney U test. Fisher's exact test was used to evaluate the differences in adverse effects between the two groups. All data were analyzed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA), and the significance level was set at $p < 0.05$.

RESULTS

Demographic and clinical characteristics of subjects

The demographic and clinical features of 42 patients with PD are summarized in Table 1. The mean (± standard deviation) age at DBS surgery was 56.9 ± 7.7 years in the STN DBS group and 57.9 ± 8.4 years in the GPi DBS group (p = 0.70). The mean age at onset of PD motor symptoms and the mean disease duration at the time of DBS surgery were not different between the two groups. The UPDRS total and part III scores were not different before DBS surgery between the two groups. At baseline, the bradykinesia subscore of the UPDRS part III and the dyskinesia subscore of the UPDRS part IV were significantly higher in the GPi DBS group than those in the STN DBS group (p = 0.01 and p < 0.01, respectively). The high UPDRS part IV subscore was mainly driven by severe dyskinesia in the GPi DBS group.

Table 1. Demographic and baseline characteristics of patients with Parkinson's disease who underwent surgery for DBS

	GPi DBS (n = 14)	STN DBS (n = 28)	p value
Female sex, n (%)	7 (50.0)	21 (75.0)	0.165
Age at operation (year), mean ± SD	57.9 ± 8.4	56.9 ± 7.7	0.701
Disease duration (year), mean ± SD	11.9 ± 3.7	11.4 ± 3.4	0.667
Age at onset (year), mean ± SD	47.0 ± 9.1	46.5 ± 8.8	0.865
Subtypes, n (%)			0.772
TD	1 (7.1)	4 (14.3)	
Intermediate	3 (21.4)	4 (14.3)	
PIGD	10 (71.4)	20 (71.4)	
UPDRS total, mean ± SD	91.1 ± 20.1	77.8 ± 18.3	0.031*
UPDRS part I, mean ± SD	5.4 ± 3.5	3.8 ± 2.9	0.158
UPDRS part II, mean ± SD	26.4 ± 7.7	22.0 ± 7.5	0.079
UPDRS part III, mean ± SD	49.0 ± 10.5	44.6 ± 11.6	0.153
Bradykinesia	23.7 ± 4.5	19.4 ± 5.5	0.013*
Tremor	3.9 ± 3.4	3.8 ± 4.4	0.654
Rigidity	9.0 ± 3.1	10.0 ± 2.9	0.665
Speech	1.8 ± 0.8	1.5 ± 0.7	0.186
Gait disturbance/postural instability	6.9 ± 2.7	5.8 ± 2.2	0.262
UPDRS part IV, mean ± SD	10.4 ± 3.6	7.5 ± 2.1	0.010*
Dyskinesia	5.1 ± 2.4	2.9 ± 1.8	0.003*
Fluctuation	3.6 ± 1.3	3.3 ± 1.2	0.458
Others	0.9 ± 1.1	0.6 ± 0.8	0.544
LED (mg), mean ± SD	1317.2 ± 382.3	1268.1 ± 468.1	0.463

The subscores for bradykinesia (summation of UPDRS items 23–27 and 31), tremor (summation of UPDRS items 20 and 21), rigidity (UPDRS item 22), speech (UPDRS item 18), and gait disturbance/postural instability (summation of UPDRS items 28–30) were assessed. The subscores for dyskinesia (summation of UPDRS items 32–35) and motor fluctuation (summation of UPDRS items 36–39) were also assessed. *p value < 0.05. GPi: globus pallidus interna, STN: subthalamic nucleus, DBS: deep brain stimulation, TD: tremor dominant, PIGD: postural instability and gait difficulty, UPDRS: Unified Parkinson's Disease Rating Scale, LED: levodopa equivalent dose, SD: standard deviation.

Comparison of DBS effects on motor symptoms

At 12 months after DBS surgery, the mean changes in the UPDRS total and individual part I–IV scores improved significantly in both the GPi and STN DBS groups, without any difference in the DBS effects between the two groups (Table 2). However, the subscores for gait disturbance/postural instability and dyskinesia were significantly more improved after GPi DBS compared with those after STN DBS (p = 0.02 and 0.02, respectively) (Table 2). The improvement in the scores for motor fluctuation was not different between the two groups (p = 0.79). LED was significantly more reduced in patients with PD after STN DBS than in those after GPi DBS (p < 0.01) (Table 2).

Comparison of adverse effects of DBS

Serious adverse events occurred in 14.3% of patients undergoing GPi DBS and in 21.4% of those undergoing STN DBS. Intracranial hemorrhage occurred in 1 patient undergoing STN DBS. Serious adverse events, including intracranial hemorrhage, did not differ significantly between the two groups (p = 0.70) (Table 3).

DISCUSSION

Our study suggests that patients with advanced PD had similar improvement in motor symptoms and profiles of adverse effects after either GPi or STN DBS but showed differential effects for certain clinical features. In this study, GPi DBS provided more beneficial effects than STN DBS on the symptoms of gait disturbance/postural instability and dyskinesia in patients with advanced PD. In contrast, LED was more reduced in patients with PD who received STN DBS than in those who received GPi DBS. These findings may be useful for designing individualized therapies for patients with advanced PD.

In general, bilateral GPi and STN DBS may be equally effective for treating PD motor symptoms and motor complications.[4,11] Physicians should freely choose between these two sites to deliver neurostimulation, although the STN has been considered to be the most effective brain target for DBS in patients with advanced PD based on data from nonrandomized, open-label, or nonblinded studies that did not compare outcomes with those of GPi DBS.[12-18] In ad-

Table 2. Changes in the UPDRS scores and LED between baseline and 12 months after surgery for DBS

	GPi DBS (*n* = 14)			STN DBS (*n* = 28)			At baseline–at 12 months		
	At baseline (off medication)	At 12 months (off medication–on stimulation)	*p* value	At baseline (off medication)	At 12 months (off medication–on stimulation)	*p* value	GPi DBS (*n* = 14)	STN DBS (*n* = 28)	*p* value
UPDRS total, mean ± SD	91.1 ± 20.1	54.0 ± 23.1	< 0.001*	77.8 ± 18.3	47.4 ± 17.9	< 0.001*	37.1 ± 16.6	30.3 ± 19.8	0.274
UPDRS part I, mean ± SD	5.4 ± 3.5	3.2 ± 3.0	0.069	3.8 ± 2.9	2.4 ± 1.7	0.034*	2.1 ± 3.5	1.4 ± 3.1	0.459
UPDRS part II, mean ± SD	26.4 ± 7.7	16.0 ± 8.1	0.001*	22.0 ± 7.5	14.3 ± 7.1	< 0.001*	10.4 ± 6.2	7.7 ± 7.2	0.236
UPDRS part III, mean ± SD	49.0 ± 10.5	29.0 ± 12.4	< 0.001*	44.6 ± 11.6	26.6 ± 11.0	< 0.001*	20.0 ± 9.7	18.0 ±13.9	0.548
Bradykinesia	23.7 ± 4.5	14.9 ± 6.0	< 0.001*	19.4 ± 5.5	13.1 ± 6.2	< 0.001*	8.8 ± 4.0	6.3 ± 7.7	0.109
Tremor	3.9 ± 3.4	1.4 ± 1.4	0.046*	3.8 ± 4.4	1.6 ± 2.0	0.150	2.6 ± 2.7	2.2 ± 4.0	0.409
Rigidity	9.0 ± 3.1	4.8 ± 3.7	0.003*	10.0 ± 2.9	3.9 ± 2.8	< 0.001*	4.2 ± 3.6	6.1 ± 3.6	0.155
Speech	1.8 ± 0.8	1.9 ± 0.9	0.899	1.5 ± 0.7	1.3 ± 0.8	0.360	-0.1 ± 1.0	0.3 ± 0.7	0.372
Gait disturbance/ postural instability	6.9 ± 2.7	3.6 ± 3.2	0.003*	5.8 ± 2.2	4.3 ± 2.8	0.034*	3.2 ± 2.2	1.5 ± 2.3	0.024*
UPDRS part IV, mean ± SD	10.4 ± 3.6	5.8 ± 2.6	0.001*	7.5 ± 2.1	4.2 ± 2.6	< 0.001*	4.6 ± 3.3	3.3 ± 2.9	0.222
Dyskinesia	5.1 ± 2.4	1.9 ± 1.4	< 0.001*	2.9 ± 1.8	1.4 ± 1.6	0.001*	3.2 ± 2.1	1.5 ± 2.0	0.016*
Fluctuation	3.6 ± 1.3	3.1 ± 1.1	0.216	3.3 ± 1.2	2.5 ± 1.8	0.051	0.5 ± 1.3	0.8 ± 2.0	0.786
Others	0.9 ± 1.1	0.8 ± 0.7	0.785	0.6 ± 0.8	0.4 ± 0.6	0.297	0.1 ± 0.7	0.3 ± 0.9	0.340
LED (mg), mean ± SD	1317.2 ± 382.3	1260.2 ± 261.6	0.650	1268.1 ± 468.1	830.6 ± 331.4	< 0.001*	57.0 ± 219.2	437.5 ± 483.6	0.004*

The subscores for bradykinesia (summation of UPDRS items 23–27 and 31), tremor (summation of UPDRS items 20 and 21), rigidity (UPDRS item 22), speech (UPDRS item 18), and gait disturbance/postural instability (summation of UPDRS items 28–30) were assessed. The subscores for dyskinesia (summation of UPDRS items 32–35) and motor fluctuation (summation of UPDRS items 36–39) were also assessed. **p* value < 0.05. GPi: globus pallidus interna, STN: subthalamic nucleus, DBS: deep brain stimulation, UPDRS: Unified Parkinson's Disease Rating Scale, LED: levodopa equivalent dose, SD: standard deviation.

dition, a recent study that investigated 36-month outcome data of DBS showed continued excellent motoric benefit from DBS, independent of target choice.[5]

Despite the overall similarity in the therapeutic response of patients with PD to DBS at both GPi and STN targets, the differential effects of DBS targets on specific clinical features of PD have also been reported. In a recent report, patients with tremor-dominant PD had a greater response to GPi DBS than to STN DBS, with improvement in gait accounting for this difference.[19] A reduction in letter verbal fluency occurred more frequently after STN DBS than after GPi DBS.[20] Additionally, depression worsened after STN DBS and improved after GPi DBS.[4] The use of the STN as a target for DBS may provide a greater chance for medication reduction,[5] although GPi DBS may provide greater flexibility in medication adjustment after DBS surgery.[5] Therefore, uncertainty about brain target selection for DBS in individual patients with PD still exists. Furthermore, the effects of DBS may be different among patients because of the heterogeneity of PD, ethnic differences, and the medications used after DBS surgery, which may differ by region.[21,22] Indeed, most well-conducted comparative studies of DBS targets have focused on Caucasian populations in European and North American countries. Therefore, outcome data from Asian populations are needed to provide the best personalized therapy for patients with advanced PD.

Table 3. Comparison of serious adverse effects between GPi and STN DBS surgery

	GPi DBS (*n* = 14)	STN DBS (*n* = 28)	*p* value
Any serious adverse events, *n* (%)	2 (14.3)	6 (21.4)	0.697
Fall	0 (0.0)	1 (3.6)	> 0.999
Depression	0 (0.0)	1 (3.6)	> 0.999
Transient severe dyskinesia	1 (7.1)	0 (0.0)	0.333
Suicide attempt	0 (0.0)	1 (3.6)	> 0.999
Median neuropathy	0 (0.0)	1 (3.6)	> 0.999
Wound adhesion	0 (0.0)	1 (3.6)	> 0.999
Cerebral infarction	1 (7.1)	0 (0.0)	0.333
Intracranial hemorrhage	0 (0.0)	1 (3.6)	> 0.999

GPi: globus pallidus interna, STN: subthalamic nucleus, DBS: deep brain stimulation.

In this study, patients with PD showed significantly greater improvement in scores for gait disturbance/postural instability after GPi DBS compared with those after STN DBS. In our patients with PD, there was no significant difference before DBS surgery in

the gait disturbance/postural instability scores between the patients in the GPi and STN DBS groups. This finding was consistent with that of a previous study that reported a greater improvement in gait scores after GPi DBS than in those after STN DBS.[19] Furthermore, previous studies also reported that STN DBS was associated with selective post-operative deterioration of gait, although other global outcome scores continued to improve.[15,23-27] Misplacement of electrodes dorsal and anterior to the STN was associated with post-operative gait deterioration in some patients with PD after STN DBS.[24] In this study, although global motor features significantly improved after STN DBS, a quantitative evaluation of electrode placement using post-surgery MRI is required to solve this issue. DBS affects gait at multiple levels of the cortex and brainstem, with simultaneous involvement of striato-frontal motor circuits and pallido-nigrofugal projections to the mesencephalic locomotor region, including the pedunculopontine nucleus.[27] Gait is a complex task requiring a delicate balance between various interacting neuronal systems.[28] Normal gait necessitates not only automatic movement processes involving stepping and balancing but also attention, afferent information processing, and intentional adjustment.[28-31] Considering the highly complex physiology and neuronal processes of gait, the exact mechanisms of the better improvement in gait disturbance after GPi DBS than in that after STN DBS are unlikely to be simple, but further clinical and experimental studies are needed to clarify these issues.

In this study, levodopa-induced dyskinesia was more improved after GPi DBS compared with that after STN DBS. Interestingly, patients with PD treated with GPi DBS received much more LED than those treated with STN DBS at 12 months after DBS surgery. This finding may suggest that patients with PD could receive much more LED without dyskinesia after GPi DBS than after STN DBS. Consistent with our findings, a previous randomized study demonstrated that GPi DBS reduced dyskinesia more effectively than STN DBS. Other case series reported that GPi DBS provided rescue therapy for refractory dyskinesias following effective STN DBS.[32,33] Dyskinesia has been associated with reduced pallidal firing rates, altered firing patterns, and increased pallidal neuronal synchronization at low frequencies.[34-37] Thus, the effect of GPi DBS on dyskinesia in patients with PD may be supported by the literature regarding the pathogenic mechanisms of dyskinesia. In contrast to these findings, other studies reported that patients with PD had similar improvements in levodopa-induced dyskinesia following either GPi or STN DBS.[4,5,19] Therefore, further studies are needed to investigate the precise effects of DBS on dyskinesia based on the target regions.

In this study, compared with patients who received GPi DBS, patients with PD had a greater reduction in LED after STN DBS. Medication reduction can have several advantages in the management of patients with PD, including desirable drug compliance, reduced drug adverse effects, and better quality of life.[38] However, medication reduction may not be desirable for some patients with PD because it may worsen apathy and decrease motivation. Therefore, the advantages and disadvantages of a greater LED reduction after STN DBS need further investigation.

This study has some limitations. First, the clinical data of the patients with PD were analyzed retrospectively. However, the clinical features of all study subjects were systemically evaluated pre- and post-operatively, using the same institutional guidelines for DBS surgery for patients with PD. Second, GPi or STN DBS surgery was not randomly selected. The brain targets for DBS surgery were determined by a consensus decision made by physicians, patients, and their caregivers in clinical practice. The non-randomization of targets may cause selection bias, especially for pre-surgery cardinal motor features. However, the pre-surgery UPDRS scores were comparable between the GPi and STN groups; the GPi and STN DBS surgeries were performed after the same pre-operative evaluation protocol; and the surgical procedures for both targets were performed by one neurosurgeon based on institutional guidelines. Third, the non-motor features of PD were not assessed in detail, which should be considered in future comprehensive studies. Fourth, the follow-up examination of the patients occurred within a relatively short period. Future studies with well-designed long-term comparisons between treatments in patients with advanced PD are needed to solve these practical issues.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.17001.

Conflicts of Interest

The authors have no financial conflicts of interest.

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