SW2-Year Outcomes of Subthalamic Deep Brain Stimulation for Idiopathic Parkinson's Disease†

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† *Presented in The Neurosurgical Association of Thailand update course: Do's & Dont's in neurosurgery. Bangkok, Thailand: 6-8 May 2008*
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Background: *Deep brain stimulation of the subthalamic nucleus (STN-DBS) is the recent surgical treatment of choice for patients with idiopathic Parkinson's disease (PD) complicated by motor fluctuation and disabling dyskinesia.*
Objective: *To study 2 years clinical outcomes, changes of medication and complications following STN-DBS in patients with advanced PD.*
Material and Method: *Twenty-seven patients with 2-year follow-up and complete data were enrolled for retrospective evaluation of Unified Parkinson's Disease Rating Scale (UPDRS) and levodopa equivalent dose (LED). Postoperative UPDRS at 6-month, 1-year and 2-years were compared with the preoperative corresponding UPDRS. Postoperative LED at 2 years was compared with the preoperative baseline. Statistical analysis was performed with paired t-test. Additionally, 62 patients with STN-DBS were enrolled for evaluation of treatment complications.*
Results: *Of 27 patients with complete 2-years follow-up, preoperative dopamine challenge test showed 50.6% improvement of motor score (UPDRS axis III). Mentation, behavior and mood (UPDRS axis I) were not significantly improved in each subscore, but significantly improved in the total score. Marked improvement of activities of daily living (UPDRS axis II) and complications of therapy (UPDRS IV) was found. Two-year postoperative motor score (UPDRS axis III) during "off medication-on stimulator" showed progressive and dramatic improvement by mean of 59.83%. The present study also revealed significant improvement of motor score (UPDRS axis III) during "on medication-on stimulator" in some items. A significant 33.4% reduction of LED was noted. Of 62 patients with bilateral STN-DBS, there was 1 asymptomatic intracerebral hemorrhage (0.8% per side), 2 speech difficulty (3.2%), 1 transient confusion (1.6%), 2 transient hypomania (3.2%), 1 stimulation induced hemiballism (1.6%), 1 wound infection (1.6%) and 1 lead malposition (0.8% per side).*
Conclusion *STN-DBS is a safe and effective treatment for PD complicated by motor fluctuation or dyskinesia. The operative outcomes show long-term improvement of activities of daily living, motor function and reduction of medication and drug-related complications.*

Keywords: *Parkinson's disease, Subthalamic nucleus, Deep brain stimulation*

J Med Assoc Thai 2010; 93 (5): 529-40
Full text. e-Journal: *http://www.mat.or.th/journal*

Idiopathic Parkinson's disease (PD) is a common movement disorder mainly treated pharmacologically. The common drugs for the disease, such as levodopa and dopamine agonists are able to provide symptomatic control in the first 5-10 years of treatment[1]. Long-term medical treatment is usually complicated with motor fluctuation between "off" and "on" periods, and often accompanied with disabling dyskinesia[2]. The "off" period is referred to as "off-medication" (the medication is not working with presence of symptoms of Parkinsonism). Contrary to the off period, "on" is a period with improvement of the indicators of mobility caused by the medication. The apparent complications of chronic levodopa administration, mainly dyskinesias

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and on-off fluctuation led to a modern era of surgical treatment for PD.

Experimental data in animal models of PD have shown abnormal neuronal hyperactivity in the subthalamic nucleus (STN) and globus pallidus interna causing parkinsonism through direct and indirect pathways of basal ganglia-thalamic-cortical circuit[3-5]. In the 1980s, surgical treatment was focused on ablation of the globus pallidus interna, pallidotomy, resulting in good effects on contralateral tremor, rigidity and dyskinesia[6]. However, bilateral pallidotomies carried risks of significant speech and cognitive impairment. High frequency electrical stimulation of the STN by deep brain stimulation (DBS) was introduced as a novel treatment in the 1990s[2]. It inhibits neuronal hyperactivity, mimicking the effect of the ablative procedure[7], but without permanent neuronal damage and allows for safe bilateral procedures[1]. Recently, STN-DBS has been the preferred surgical procedure of choice for patients with advanced Parkinson's disease[8].

The authors studied long-term outcomes of STN-DBS in Thai patients with PD at 2 years post-operatively.

Material and Method

Patient population

Since 2004, the presented group has conducted over 300 procedures in 153 patients with various movement disorders. The STN-DBS for PD is the most common procedure. All of the presented 62 patients with STN-DBS were enrolled for study of surgical complications and 27 patients who had 2-years complete follow-up with complete data were selected for retrospective evaluation of Unified Parkinson's Disease Rating Scale (UPDRS) and levodopa equivalent dose (LED). The present study was approved by Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand.

The selection criteria of STN-DBS were clinically diagnosed idiopathic PD with significant disabling motor fluctuation, dyskinesia or tremor despite optimization of medications. In addition, physical age should not be too old and pre-operative levodopa challenge test should exhibit at least 30% improvement of motor score assessed with UPDRS axis III, except for tremor, dopaminergic non-responsive symptoms such as "on period" speech difficulty, freezing and falling, which should not be the major source of disability as they will not improve after surgery. The exclusion criteria included significant brain atrophy, diffuse white matter lesions, severe dementia, major psychiatric disorders such as unsolved major depression or psychosis, secondary Parkinsonism, general contraindications for surgery such as inappropriate medical conditions and coagulopathy.

Clinical assessment

All patients were clinically evaluated with the UPDRS. Mean UPDRS axis I to IV were scored before the operation, at 6 months, 1 year and 2 years postoperatively by independent observers. Particularly for the mean motor score (UPDRS axis III), the patients were pre-operatively assessed in two conditions, "off medication" and "on medication". Similarly, mean postoperative UPDRS axis III during "off medication-on stimulation" and "on medication-on stimulation" were collected at 6 months, 1 year, and 2 years. The postoperative mean UPDRS of each time was compared with the equivalent pre-operative mean UPDRS. Lower scores of UPDRS indicate better performance.

Pre-operative and 2-year postoperative information about dosage of drugs was also collected. Both of them were calculated as LED and compared. A LED equals 100 mg of levodopa or 133 mg of levodopa modified release preparations or 1 mg of pergolide or 10 mg of bromocriptine or 1 mg of cabergolide or 1 mg of lisuride or 20 mg of apomorphine.

Surgical procedure

The patients were operated on under local anesthesia and stereotactic guidance. Direct STN targeting was done by T2W axial and coronal acquisition MRI. Stereotactic planning software was used for CT-MRI fusion, reconstruction of images adjusted to be orthogonal to the plane of anterior commissure-posterior commissure (AC-PC), and for calculation of stereotactic coordinate and planning of a proper trajectory. Micro-electrode recording, macro-stimulation with micro-electrode cannula and macro-stimulation with DBS lead were sequentially performed. The appropriate target should have an adequate length of the STN for at least 4.5 mm, contain movement-related cells and exhibit no adverse effects during macro-stimulation (amplitude 3.5 mA, pulse width (PW) 60 microseconds, frequency 130 Hz for 291 micro-electrode cannular macro-stimulation and amplitude 4 V, PW 60 microseconds, frequency 130 Hz, contact 0- 3+ for 3389 lead macrostimulation).

Statistical analysis

The primary outcome was changed in UPDRS and the secondary outcome was a change in LED. Data, which approximated a normal distribution, will be presented as mean and standard deviation. Changes between preoperative baseline, 6-months, 1-year, and 2-years follow-up were analyzed by using paired t-test. This analysis was repeated for "off medication" and "on medication" period in each clinical parameter for only the UPDRS axis III. A p-value < 0.05 is considered to be statistically significant. All data have been analyzed by using SPSS for Windows Release 11.0.0 Standard Version.

Results

Demographic data are shown in Table 1. The majority of the patients had no associated disease. The common symptoms were rigidity, resting tremor and bradykinesia, respectively.

Pre-operative dopamine challenge test revealed dramatic improvement of mean motor score (UPDRS axis III) accounting for 50.58% (Table 2).

Table 1. Demographic characteristics

Characteristics	Numbers (%)
Number of patients	27
Gender	
Male	13 (48.1%)
Female	14 (51.9%)
Age of onset (years)	
Mean $\pm$ SD	40.59 $\pm$ 7.55
Range	27-64
Duration (years)	
Mean $\pm$ SD	10.89 $\pm$ 3.45
Range	5-17
Age of surgery (years)	
Mean $\pm$ SD	51.67 $\pm$ 7.44
Range	37-76
Underlying diseases	
Diabetes mellitus	1 (3.7%)
Dyslipidemia	1 (3.7%)
Preoperative symptoms	
Rigidity	24 (88.9%)
Resting tremors	19 (70.4%)
Bradykinesia	17 (63.0%)
Dystonia	9 (33.3%)
Akinesia	7 (25.9%)
Postural instability	6 (22.2%)
Action tremors	3 (11.1%)
Pain	3 (11.1%)

Speech was the only subscore which did not statistically improve with the challenge test.

Total subscore of mentation, behavior and mood (UPDRS axis I) improved after six months. However, each item did not significantly improve and the thought disorder subscore was sometimes insignificantly worse than the pre-operation (Table 3).

Total subscores of the activities of daily living (UPDRS axis II) and most of its items became significantly better than those pre-operation. Bulbar functions (speech, swallowing and salivation) tended to improve less than limb motor functions (Table 4).

Total subscore of motor function (UPDRS axis III) and all of its items during "off medication-on stimulator" significantly improved up to 2 years, except speech performance which was insignificantly improved (Table 5). Posture and instability had the least magnitude of improvement among all items. Although most items of motor subscores during "on medication-on stimulator" did not significantly improve, upper limb rigidity, some upper limb functions and performances of axial control (arising from a chair, posture and instability) consistently improved postoperatively (Table 6).

There was marked improvement of drug-induced dyskinesia or dystonia assessed by UPDRS axis IV. Motor fluctuation significantly improved with 86.36% reduction of "Off" duration. Unpredictability and suddenly "off" completely disappeared after the operation, whereas anorexia, sleep problem and orthostasis remained unchanged (Table 7).

Mean preoperative LED was 7.25 $\pm$ 3.36 LED/day, ranging from 1.5-15 LED/day. Postoperative LED at 2 years revealed a significant reduction to 4.83 LED/day ($p < 0.01$). Overall reduction of LED was 30.63%. This effect resulted in a decrease of postoperative drug-induced motor complications. Of 27 patients, 19 patients (70.37%) could reduce their daily LED; 3 patients (11.11%) were able to completely discontinue their daily LED and 5 patients (18.52%) had no change.

Of 62 patients with bilateral STN-DBS, there were 1 asymptomatic intracerebral hemorrhage (0.8% per side), 2 speech difficulty (3.2%), 1 transient confusion (1.6%), 2 transient hypomania (3.2%), 1 stimulation induced hemiballism (1.6%), 1 wound infection (1.6%). The authors found only 1 lead malposition (0.8% per side) in an early case, whereas stimulation-induced dementia, stimulation-induced depression, lead migration and broken lead have not been encountered.

Table 2. The preoperative mean UPDRS axis III (dopamine challenge test)

	"Off" medication	"On" medication	p-value
UPDRS III			
Speech	1.00 ± 1.00	0.78 ± 0.64	0.136
Facial expression	1.70 ± 0.87	1.11 ± 0.70	<0.01*
Resting tremor	0.81 ± 1.07	0.19 ± 0.39	<0.01*
Hand agility	1.52 ± 1.31	0.48 ± 0.75	<0.01*
Foot agility	0.89 ± 0.89	0.22 ± 0.51	<0.01*
Action tremor	1.04 ± 0.94	0.35 ± 0.48	<0.01*
Neck rigidity	1.41 ± 1.05	0.63 ± 0.74	<0.01*
Upper limb rigidity	2.24 ± 1.01	1.06 ± 0.79	<0.01*
Lower limb rigidity	1.78 ± 0.97	0.74 ± 0.66	<0.01*
Finger tapping	2.07 ± 0.87	1.11 ± 0.75	<0.01*
Handgrip	1.81 ± 0.79	1.00 ± 0.78	<0.01*
Pronation-supination	1.93 ± 1.18	0.85 ± 0.77	<0.01*
Leg agility	1.85 ± 1.23	0.70 ± 0.72	<0.01*
Arise from chair	1.79 ± 1.32	0.89 ± 0.97	0.02*
Posture	2.06 ± 1.16	1.04 ± 0.94	<0.01*
Instability	1.85 ± 1.23	1.26 ± 0.98	0.02*
Gait	2.26 ± 1.16	1.22 ± 0.97	<0.01*
Bradykinesia	2.37 ± 1.15	1.04 ± 0.85	<0.01*
Total subscore	45.91 ± 13.98	22.69 ± 10.43	<0.01*

* Indicates statistically significant improvement (p-value < 0.05)
# Indicates worsening of the subscore after on-medication

Table 3. The preoperative and postoperative mean UPDRS axis I

	Preoperative	6-month score and p-value	1-year score and p-value	2-year score and p-value
Mentation	0.11 ± 0.32	0.08 ± 0.28 0.574	0.08 ± 0.28 0.574	0.08 ± 0.28 0.574
Thought disorder	0.11 ± 0.32	0.24 ± 0.59 0.212	0.08 ± 0.28 0.574	0.12 ± 0.33# 0.664
Depression	0.44 ± 0.64	0.36 ± 0.70 0.203	0.36 ± 0.57 0.161	0.36 ± 0.57 0.161
Motivation	0.11 ± 0.32	0.08 ± 0.27 0.574	0.11 ± 0.32 1.000	0.00 ± 0.00 0.083
Total subscore	0.78 ± 0.97	0.76 ± 0.25 0.641	0.64 ± 0.99 0.031*	0.56 ± 0.77 0.025*

* Indicates significant improvement (p-value < 0.05)
# Indicates worsening of the postoperative subscore

Discussion

Demographic data

The majority of the patients in the present study were young-onset PD with a mean age of 51.67 years which was relatively younger than that of other studies[2,6,9]. Long duration of the disease was revealed by a mean duration of 10.89 years before surgery. Other studies showed mean age of the operation ranging from 55.0 to 60.9 years and mean duration of the disease up to 15 years[2,6,9].

Preoperative assessment

The most common symptom was rigidity followed by resting tremor and bradykinesia,

Table 4. The preoperative and postoperative UPDRS axis II

	Preoperative	6-month score and p-value	1-year score and p-value	2-year score and p-value
Speech	1.04 ± 0.89	0.69 ± 0.79 0.166	1.04 ± 0.95 1.000	0.58 ± 0.58 0.015*
Salivation	0.89 ± 0.75	0.54 ± 0.51 0.203	0.65 ± 0.74 0.627	0.33 ± 0.61 <0.03*
Swallowing	0.43 ± 0.63	0.23 ± 0.51 0.486	0.23 ± 0.51 0.486	0.19 ± 0.40 0.306
Handwriting	1.85 ± 0.91	0.73 ± 0.83 <0.01*	0.85 ± 0.73 <0.01*	0.58 ± 0.64 <0.01*
Cutting food	1.74 ± 0.98	0.50 ± 0.86 <0.01*	0.62 ± 0.32 <0.01*	0.46 ± 0.58 <0.01*
Dressing	1.93 ± 0.99	1.04 ± 1.11 <0.01*	0.92 ± 0.97 <0.01*	0.58 ± 0.60 <0.01*
Hygiene	2.00 ± 1.11	0.88 ± 0.99 <0.01*	0.88 ± 0.95 <0.01*	0.72 ± 0.80 <0.01*
Turning in bed	1.93 ± 1.38	1.00 ± 1.23 <0.01*	0.81 ± 1.20 <0.01*	0.73 ± 1.00 <0.01*
Falling	1.07 ± 1.35	0.46 ± 1.03 0.032*	0.54 ± 0.90 0.056	0.50 ± 0.76 0.035*
Freezing	1.89 ± 1.19	1.04 ± 1.11 <0.01*	0.77 ± 1.03 <0.01*	0.65 ± 0.89 <0.01*
Walking	2.26 ± 0.98	0.73 ± 0.72 <0.01*	0.58 ± 0.85 <0.01*	0.62 ± 0.57 <0.01*
Tremor	1.63 ± 1.15	0.58 ± 0.76 <0.01*	0.46 ± 0.64 <0.01*	0.54 ± 0.70 <0.01*
Sensory	0.56 ± 0.85	0.35 ± 0.69 0.136	0.31 ± 0.55 0.090	0.35 ± 0.56 0.056
Total subscore	17.50 ± 9.14	8.73 ± 6.87 <0.01*	8.31 ± 6.95 <0.01*	6.88 ± 4.93 <0.01*

* Indicates significant improvement (p-value < 0.05)
# Indicates worsening of the postoperative subscore

respectively. Pre-operative levodopa challenge test revealed a dramatic improvement of motor score (UPDRS axis III) in all patients by mean of 50.6%. Therefore, all patients were considered to be good candidates for STN-DBS. The UPDRS axis II exhibited fair performances in activities of daily living (ADL). Drug-induced dyskinesia and motor fluctuation were the major complications of medical treatment.

Postoperative UPDRS axis I

Most parameters in the UPDRS axis I were not significantly changed from the pre-operative counterparts. Thought disorder seemed to be insignificantly worse. Interestingly, a significant improvement of the total subscore was demonstrated at 1-year and 2-years postoperatively. There was no development of postoperative depression in the presented patients while many studies showed development of depressive episodes following STN-DBS[10-13]. Berney et al revealed a high rate of major depressive episodes occurring within the first year following STN-DBS for late-stage PD[10]. A large series of systematic analysis of 1398 patients with STN-DBS showed 41% of cognitive alteration, 8% of depression and 4% of hypomania[11]. Patients with clinically relevant behavioral alterations before STN-DBS can be at risk of further mental deterioration after the surgery[11]. Perriol et al showed 5% of patients developing postoperative dysthymic episode not associated with cognitive decline[12]. Bejjani et al reported a case of a 65-year-old woman who developed an acute depressive episode after turning on of contact 0 DBS located in the central part of the *substantia nigra*, 2 mm below contacts 1 and 2 in the

Table 5. Comparison of the mean UPDRS axis III during "off medication-on stimulator"

	Mean UPDRS III, percentage of improvement and p-value			
	Preoperative	6-month	1-year	2-year
Speech	1.00	1.40	1.16	1.00
		-40.00%[#]	-16.00%[#]	0%
		0.036	0.503	1.00
Facial expression	1.70	1.64	1.36	1.28
		3.50%	20.00%	24.70%
		0.574	0.029*	<0.01*
Resting tremor	0.81	0.76	0.52	0.48
		6.20%	35.80%	40.70%
		0.450	<0.01*	<0.01*
Hand agility	1.52	1.16	0.96	0.92
		23.70%	36.80%	39.47%
		0.013*	<0.01*	<0.01*
Foot agility	0.89	0.64	0.44	0.40
		28.09%	50.56%	55.06%
		<0.01*	<0.01*	<0.01*
Action tremor	1.04	0.76	0.60	0.52
		26.92%	42.31%	50.00%
		0.032*	<0.01*	<0.01*
Neck rigidity	1.41	0.96	0.92	0.80
		31.91%	34.75%	43.26%
		<0.01*	<0.01*	<0.01*
Upper limb rigidity	2.27	1.68	1.44	1.28
		25.99%	36.56%	43.61%
		<0.01*	<0.01*	<0.01*
Lower limb rigidity	1.78	1.20	1.04	1.00
		32.58%	41.57%	43.82%
		<0.01*	<0.01*	<0.01*
Finger tapping	2.07	1.52	1.20	1.08
		26.57%	42.03%	47.83%
		<0.01*	<0.01*	<0.01*
Handgrip	1.81	1.28	1.00	0.76
		29.28%	44.75%	58.01%
		<0.01*	<0.01*	<0.01*
Pronation-supination	1.93	1.36	1.16	1.04
		29.53%	39.90%	46.11%
		<0.01*	<0.01*	<0.01*
Leg agility	1.85	1.16	1.04	0.96
		37.30%	43.78%	48.11%
		<0.01*	<0.01*	<0.01*
Arise from chair	1.79	1.40	1.24	1.16
		21.79%	30.73%	35.20%
		<0.01*	<0.01*	<0.01*
Posture	2.06	1.88	1.80	1.56
		8.74%	12.62%	24.27%
		0.095	0.012*	<0.01*
Instability	1.85	1.85	1.64	1.44
		0%	11.35%	22.16%
		0.478	0.058	<0.01*
Gait	2.26	1.80	1.56	1.48
		20.35%	30.97%	34.51%
		<0.01*	<0.01*	<0.01*
Bradykinesia	2.37	1.60	1.40	1.28
		32.49%	40.93%	45.99%
		<0.01*	<0.01*	<0.01*
Total subscore	45.91	24.04	20.52	18.44
		47.64%	55.30%	59.83%
		<0.01*	<0.01*	<0.01*

* Indicates significant improvement (p-value < 0.05)

[#] Indicates worsening of the subscore

Table 6. Comparison of the mean UPDRS axis III during "on medication-on stimulator"

	Mean UPDRS III, percentage of improvement and p-value			
	Preoperative	6-month	1-year	2-year
Speech	0.78	0.65	0.78	0.78
		16.67%	0%	0%
		0.327	1.00	1.00
Facial expression	1.11	1.00	1.00	0.96
		9.91%	9.91%	13.51%
		0.327	0.276	0.256
Resting tremor	0.19	0.12	0.19	0.12
		36.84%	0%	36.84%
		0.161	1.00	0.161
Hand agility	0.48	0.35	0.31	0.27
		27.08%	35.42%	43.75%
		0.043*	0.022*	0.011*
Foot agility	0.22	0.22	0.15	0.15
		0.00%	31.82%	31.82%
		1.00	0.327	0.327
Action tremor	0.38	0.23	0.27	0.27
		39.47%	28.95%	28.95%
		0.03*	0.083	0.083
Neck rigidity	0.63	0.42	0.42	0.38
		33.33%	33.33%	43.26%
		0.83	0.56	<0.01*
Upper limb rigidity	1.06	0.81	0.88	0.88
		23.58%	16.98%	16.98%
		0.073	0.047*	0.047*
Lower limb rigidity	0.74	0.58	0.62	0.50
		21.62%	16.22%	32.43%
		0.265	0.327	0.022*
Finger tapping	1.11	0.81	0.92	0.88
		27.03%	17.12%	20.72%
		0.018*	0.022*	0.031*
Handgrip	1.00	0.81	0.92	0.77
		19.00%	8.00%	23.00%
		0.170	0.327	0.056
Pronation-supination	0.85	0.73	0.77	0.69
		29.53%	39.90%	46.11%
		0.425	0.664	0.376
Leg agility	0.70	0.50	0.58	0.58
		28.57%	17.14%	17.14%
		0.265	0.574	0.574
Arise from chair	0.89	0.73	0.65	0.73
		17.98%	26.97%	17.98%
		0.022*	0.016*	0.022*
Posture	1.04	0.85	0.88	0.81
		18.27%	15.38%	22.16%
		0.134	0.043*	0.011*
Instability	1.26	1.04	1.08	1.08
		17.46%	14.29%	14.29%
		0.011*	0.022*	0.022*
Gait	1.22	1.08	1.04	1.08
		11.48%	14.75%	11.48%
		0.103	0.057	0.103
Bradykinesia	1.04	0.81	0.92	0.96
		22.16%	11.54%	7.69%
		0.016*	0.103	0.265
Total subscore	22.69	12.38	13.38	12.77
		45.44%	41.03%	43.72%
		<0.01*	<0.01*	<0.01*

* Indicates significant improvement (p-value < 0.05)

# Indicates worsening of the subscore

Table 7. Comparison of UPDRS axis IV

	Mean UPDRS III, percentage of improvement and p-value			
	Preoperative	6-month	1-year	2-year
Dyskinesia duration	1.52	0.80	0.60	0.60
		47.37%	60.53%	60.53%
		<0.01*	<0.01*	<0.01*
Dyskinesia disability	1.32	0.60	0.44	0.44
		54.55%	66.67%	66.67%
		<0.01*	<0.01*	<0.01*
Painful dyskinesia	0.20	0.24#	0.08	0.08
		-20.0%	60.00%	60.00%
		0.788	0.083	0.083
Morning dystonia	0.52	0.20	0.12	0.08
		61.54%	76.92%	84.62%
		<0.01*	<0.01*	<0.01*
"Off" predictable	0.92	0.60	0.32	0.24
		34.78%	65.22%	73.91%
		<0.01*	<0.01*	<0.01*
"Off" unpredictable	0.32	0.00	0.04	0.00
		100.00%	87.50%	100.0%
		<0.01*	<0.01*	<0.01*
"Off" suddenly	0.40	0.04	0.04	0.00
		90.00%	90.00%	100.00%
		<0.01*	<0.01*	<0.01*
"Off" duration	0.88	0.20	0.12	0.12
		77.27%	86.36%	86.36%
		<0.01*	<0.01*	<0.01*
Anorexia	0.08	0.04	0.00	0.00
		50.00%	100.00%	100.00%
		0.327	0.161	0.161
Sleep disturbance	0.40	0.36	0.28	0.36
		10.00%	30.00%	10.00%
		0.746	0.265	0.664
Orthostasis	0.16	0.16	0.04	0.00
		0%	75.00%	100.0%
		1.000	0.185	0.043*
Total subscore	6.72	3.12	2.20	1.92
		53.57%	67.26%	71.43%
		<0.01*	<0.01*	<0.01*

* Indicates significant improvement (p-value < 0.05)
# Indicates worsening of the subscore

STN. When the active contact was changed and the STN was stimulated, the symptoms of PD improved without emotional change[13].

Postoperative UPDRS axis II

The postoperative UPDRS axis II revealed dramatic improvement in almost all parameters with the exception of bulbar function (speech and swallowing), autonomic function (salivation) and sensory, which typically did not improve, following STN-DBS. Many studies also showed improvement of the UPDRS axis II after the surgery. Perriol et al reported a great improvement of ADL in 18% of patients, 40% had moderate improvement, while 42% did not display any change in the UPDRS axis II score[12]. Haffenden et al demonstrated a significant improvement of disability items (speech, handwriting, cutting food, dressing, hygiene, turning in bed, and walking) without

improvement of impairment items (salivation, swallowing, falling, freezing, tremor, and sensory symptoms) at 12-month following STN-DBS[14]. The present study also revealed a dramatic improvement of the majority of axial ADL score (turning in bed, freezing, falling, walking) resembling the study purposed by Bejjani et al[15].

Postoperative UPDRS axis III

The UPDRS axis III has been the main focus in most studies of outcome after surgery for PD. The present studies revealed a markedly progressive improvement of the UPDRS axis III especially limb symptoms during "off medication-on stimulation" though progression of PD with time. One possible reason which generates this result is that dyskinesia induced by STN stimulation inhibits progressive increasing of stimulation voltage to the optimal higher voltage: many patients needed 6 months or longer of low suboptimal voltage stimulation to achieve tolerance to stimulation-induced dyskinesia. Although average motor scores during "on medication-on stimulation" were less improved than those during "off medication-on stimulation", they were changed significantly in a few items, particularly axial symptoms (arising from a chair and postural instability) up to 24 months after STN-DBS. Rodriguez-Oros et al revealed a sustained significant improvement of motor score during "off medication-on stimulation" at 4 years postoperatively. They also showed insignificant changes of motor score during "off medication-on stimulation" at 3 years postoperatively when compared with the preoperative baseline. However, the changes were significant when compared with those of 1-year postoperatively[1]. Limousin et al showed dramatically significant improvement of motor score (60%) during "off medication-on stimulation", whereas motor score during "on medication-on stimulation" were not significantly improved (10%) at 1, 3, 6 and 12 months following STN-DBS[2]. Visser-Vandewalle et al also demonstrated a significant improvement of motor score (43%) during "off medication-on stimulation" without significant improvement (22.6%) of motor score during "on medication-on stimulation" on 4-years follow-up[6]. Many studies also showed comparable results[16-27].

Postoperative UPDRS axis IV

Dyskinesia was dramatically reduced, particularly at 2-years follow-up secondarily from marked reduction of levodopa. The items of "off" symptoms were also improved significantly. However, there were no significant changes of anorexia, sleep disturbance, and orthostasis. Many studies showed the same significant improvement of dyskinesia following STN-DBS[1,2,6,16,18,21,28,29].

The LED

Overall reduction in LED at 2-year following STN-DBS dose was 30.3% from the preoperative LED. Other studies also showed a marked reduction in levodopa and LED ranging from 22% to 81%[2,16-21,28-34]. According to a marked decrease of the LED, inevitable drug-induced motor complications, especially dyskinesia, were dramatically reduced.

Adverse effects

The most frequent adverse effects in the present study were speech difficulty and transient psychiatric problems, whereas the incidence of intracerebral hemorrhage, wound complication and hardware-related problem were quite low. Other studies showed the major complications including intracerebral hematoma, hardware-associated complications, stimulation-related adverse effects, infection and psychiatric problems, especially confusion, hypomania and depression[8,22,23,25,27,35].

Overview

When comparing the present results with other global reports, improvement of the UPDRS axis I, II, IV, and the UPDRS axis III during "off medication-on stimulation" they were comparable to other studies. However, the present study showed more improvement of UPDRS axis III during "on medication-on stimulation" and less reduction of the postoperative LED. These might reflect the authors' pre-operative "on medication" and actually might be not the best "on medication" and results in relative high preoperative "on medication" motor score (UPDRS axis III). Many patients of the present study had adverse effects from medication and thus received preoperative suboptimal dosage of medication.

Furthermore, the authors also encountered less postoperative speech worsening and depression than indicated in global reports. These might stem from the authors' surgical technique in which the authors focused mainly on complication avoidance rather than on clinical improvement. The presented macro-stimulation threshold was set to a high level of 4 Volts for targeting criteria and the most ventral contacts, contact 0, were always located at the bottom

of STN and never deeper into *substantia nigra* in order to avoid depression.

The authors usually encountered post-operative stimulation-induced dyskinesia and this problem forced the authors to increase stimulation parameters very slowly, over several months or a year. This made the presented motor improvement at 2-years better than at 1-year and 6-months, respectively, through deterioration of PD over time. However, the authors believe a longer study may show deterioration from progression of the disease.

Conclusion

STN-DBS is a safe and effective neurosurgical treatment for advanced PD. Outcomes showed dramatic improvement of the UPDRS axis II, III and IV. LED was also significantly reduced and resulted in marked improvement of levodopa-induced dyskinesia.

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ผลลัพธ์ที่เวลา 2 ปีของการรักษาโรคพาร์กินสันที่ไม่ทราบสาเหตุโดยการผ่าตัดกระตุ้นสมองส่วนลึกในซับธาลามิคนิวเคลียส

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ภูมิหลัง: *การผ่าตัดกระตุ้นสมองส่วนลึกในซับธาลามิคนิวเคลียสเป็นการรักษา ที่เป็นทางเลือกใหม่สำหรับผู้ป่วยโรคพาร์กินสันที่มีการทำงานที่ไม่แน่นอนของระบบประสาทมอเตอร์ และการเคลื่อนไหวผิดปกติแบบดิสไคนีเซีย ซึ่งเป็นอุปสรรคต่อผู้ป่วย*

วัตถุประสงค์: *เพื่อศึกษาผลลัพธ์ทางคลินิก, การเปลี่ยนแปลงขนาดของยาและผลแทรกซ้อนหลังที่ระยะเวลา 2 ปีหลังผ่าตัดกระตุ้นสมองส่วนลึกในซับธาลามิคนิวเคลียสในผู้ป่วยโรคพาร์กินสันที่เป็นมาก*

วัสดุและวิธีการ: *ผู้ป่วย 27 รายที่มีการติดตามการรักษาและมีข้อมูลสมบูรณ์ครบ 2 ปี หลังผ่าตัดถูกคัดเลือกเพื่อประเมินยูนิฟายด์พาร์กินสันดิซีสเรทติ้งสเกล (ยูพีดีอาร์เอส) และขนาดของยาที่เทียบเป็นขนาดของลีโวโดพาแบบย้อนหลัง, ยูพีดีอาร์เอสที่เวลา 6 เดือน, 1 ปี และ 2 ปีหลังผ่าตัดถูกเปรียบเทียบกับของก่อนผ่าตัดที่สอดคล้องกัน, ขนาดของยาที่เทียบเป็นขนาดของลีโวโดพาที่เวลา 2 ปีหลังผ่าตัดถูกเปรียบเทียบกับของก่อนผ่าตัด, การวิเคราะห์ทางสถิติโดยวิธีแพร์ทีเทส นอกจากนี้ผู้ป่วย 62 ราย ที่ได้รับการผ่าตัดกระตุ้นสมองส่วนลึกในซับธาลามิคนิวเคลียสถูกคัดเลือกเพื่อประเมินผลแทรกซ้อนจากการผ่าตัด*

ผลการศึกษา: *ในผู้ป่วย 27 ราย ที่ได้รับการติดตามผลการรักษาครบ 2 ปี การทดสอบโดยการให้สารโดปามีนก่อนผ่าตัดพบว่ามีการดีขึ้นของคะแนนของระบบประสาทมอเตอร์ (ยูพีดีอาร์เอส แกนที่ 3) 50.6%, ไม่มีการเปลี่ยนแปลงของความคิด, พฤติกรรมและอารมณ์ (ยูพีดีอาร์เอส แกนที่ 1) อย่างมีนัยสำคัญในแต่ละรายการคะแนนย่อย, แต่ทว่ามีการดีขึ้นของคะแนนรวมอย่างมีนัยสำคัญ, มีการดีขึ้นอย่างชัดเจนของการช่วยเหลือตนเองในชีวิตประจำวัน (ยูพีดีอาร์เอส แกนที่ 2) และผลแทรกซ้อนจากการรักษา (ยูพีดีอาร์เอส แกนที่ 4), คะแนนระบบประสาทมอเตอร์หลังผ่าตัดในช่วงหยุดยาร่วมกับเปิดเครื่องกระตุ้นที่เวลา 2 ปีหลังผ่าตัดมีการดีขึ้นเรื่อย ๆ และดีขึ้นอย่างชัดเจนโดยคิดเป็น 59.83% เทียบกับของก่อนผ่าตัด, การศึกษายังพบว่ามีการดีขึ้นของคะแนนระบบประสาทมอเตอร์หลังผ่าตัดในช่วงรับประทานยาร่วมกับเปิดเครื่องกระตุ้นในบางรายการ, พบว่ามีการใช้ยาลดลงอย่างมีนัยสำคัญ คิดเป็น 33.4% ของขนาดของยาที่เทียบเป็นขนาดของลีโวโดพา, ในผู้ป่วยจำนวน 62 ราย ที่ได้รับการผ่าตัดกระตุ้นสมองส่วนลึกในซับธาลามิคนิวเคลียสพบ 1 ราย ที่มีเลือดออกในสมองแต่ไม่มีอาการ (0.8% ต่อการผ่าตัด 1 ข้าง), 2 ราย ที่มีอาการพูดลำบาก (3.2%), 1 ราย ที่มีอาการสับสนชั่วคราว (1.6%), 2 ราย ที่มีความผิดปกติทางจิต แบบไฮโปแมเนีย (3.2%), 1 ราย ที่มีการเคลื่อนไหวผิดปกติแบบเฮมิบัลลิซึมซึ่งเกิดจากการกระตุ้น (1.6%), 1 ราย ที่มีการติดเชื้อของแผลผ่าตัด (1.6%) และ 1 รายที่มีตำแหน่งของขั้วไฟฟ้ากระตุ้นสมองไม่ดี (0.8% ต่อการผ่าตัด 1 ข้าง)*

สรุป: *การผ่าตัดกระตุ้นสมองส่วนลึกในซับธาลามิคนิวเคลียสเป็นการรักษาที่ปลอดภัย และมีประสิทธิภาพสำหรับผู้ป่วยโรคพาร์กินสันที่มี การทำงานที่ไม่แน่นอน ของระบบประสาทมอเตอร์และการเคลื่อนไหวผิดปกติแบบดิสไคนีเซีย, ผลลัพธ์การผ่าตัดแสดงการดีขึ้นของการช่วยเหลือตนเองในชีวิตประจำวัน, การทำงานของระบบประสาทมอเตอร์, การลดลงของยาและผลแทรกซ้อนที่เกี่ยวข้องกับยา*