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Clinical Article

STN DBS of Advanced Parkinson's Disease Experienced in a Specialized Monitoring Unit with a Prospective Protocol

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Objective : In the evaluation of patients with Parkinson's disease (PD), most neurologists only see their patients during a limited period of their fluctuating 24-hour-a-day lives. This study aimed to assess the short-term outcome of STN stimulation for patients with advanced PD evaluated in a 24-hour monitoring unit for movement disorder (MUMD) using a prospective protocol.

Methods : Forty-two patients with advanced PD consecutively treated with bilateral STN stimulation using multi-channel microelectrode recording were included in this study. All patients were evaluated using a 24-hour MUMD with a video recording/editing system and were evaluated with a prospective protocol of the Unified Parkinson's Disease Rating Scale, Hoehn and Yahr Staging, Schwab and England Activities of Daily Living, levodopa equivalent daily dose (LEDD), Short Form-36 Health Survey, and neuropsychological tests. Magnetic resonance (MR) images of the brain were performed prior to and six months after surgery.

Results : All patients were evaluated at three and six months after surgery. There was a rapid and significant improvement of the motor symptoms, especially in tremor and rigidity, after STN stimulation with low morbidity. Dyskinesia was markedly decreased with much lowered LEDD values by 50% after STN stimulation. 1.5T MR images were safely taken according to the manufacturer's guidelines at six months after surgery without any adverse effects in 41 patients treated with STN stimulations.

Conclusion : Evaluations in a 24-hour monitoring unit could reduce the dose of medication efficiently to an optimal level with patients' comfort and improve the clinical symptoms in harmony with STN stimulation.

KEY WORDS : Parkinson's disease · 24-hour monitoring unit for movement disorder (MUMD) · Subthalamic nucleus · Deep brain stimulation · Multi-channel parallel microelectrode recording (MER) · MR images.

INTRODUCTION

Parkinson's disease (PD) is the second most common degenerative disease affecting the central nervous system following Alzheimer's disease[21]. Soon after the introduction of deep brain stimulation (DBS) by Dr. Benabid and his colleagues in the late 1980s, the subthalamic nucleus (STN) DBS has become the preferred treatment for patients with advanced PD suffering from drug-induced side effects or motor fluctuation following the long-term use of dopaminergic drugs[2,4,7,10,14,15,17,18,23,24,27].

On the other hand, when evaluating of the patients with PD most neurologists see their patients only during examination time at outpatient clinics, which is just a short period of time during their 24-hour daily lives. Therefore, the majority of their daily life was only identified by statements described by the patients themselves, including their PD diary. This might be a pitfall in the precise evaluation of patients with advanced PD showing a number of varying and unexpectedly-appearing side effects such as the severe wearing-off phenomenon, motor fluctuation, dyskinesia and/or diphasic off-dystonia with on-dyskinesia.

A specialized 24-hour monitoring system might be needed in order to more closely monitor the actual, whole-day-long clinical status of patients with PD. Such a system might also be useful not only for the selection of surgical candidates for DBS but also for dose adjustment of anti-

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parkinsonian drugs used to treat patients with PD before and after surgery.

Therefore, the authors developed a specialized 24-hour monitoring unit for movement disorder (MUMD) equipped with monitoring cameras and a video recording/editing system with a prospective protocol to evaluate patients with PD for 24 hours a day. This study aimed to assess the effectiveness of the MUMD by analyzing the short-term outcome of STN DBS for patients with advanced PD evaluated in a 24-hour monitoring unit with a prospective protocol.

MATERIALS AND METHODS

Forty-two patients with advanced PD consecutively treated with bilateral STN DBS after being evaluated by MUMD according to a prospective protocol between March 2005 and January 2006 were included in this study (Table 1). Although 49 patients with PD were treated with STN DBS during that time, seven patients were excluded from this study because they had unilateral tremor-dominant PD, which was resistant to medical therapy.

Table 1. Characteristics of the 42 patients treated with bilateral STN stimulation*

Variable	Mean (range)
Age (yr)	58 (26-72)
Body weight (Kg)	56.3±8.9
Symptom Duration (yr)	11.1 (4-30)
Duration of medication (yr)	9.5 (3-22)
LEDD (mg/day)†	790.4±375.7
Total score of the UPDRS	
On-medication	32.4 (4.5-91.0)
Off-medication	68.4 (21.5-117.0)
Score of part III of the UPDRS	
On-medication	20.1 (2.0-59.0)
Off-medication	39.3 (9.0-78.0)
Hoehn & Yahr score	
On-medication	2.4 (1-4)
Off-medication	3.2 (1-5)
ADL	
On-medication	78.2 (30-100)
Off-medication	50.0 (10-90)
Good awake time (%)	36.6 (0-93)
Dyskinesia disability	2.6 (0-4)

There were 18 male and female patients. One of these patients had had a cardiac pacemaker for the sick sinus syndrome prior to STN DBS. Two patients had a history of previous unilateral thalamotomy. * Plus-minus values are means±SD †Levodopa equivalent daily dose was calculated for each antiparkinsonian medication by multiplying the total daily dosage of each drug by its potency relative to a standard levodopa preparation assigned the value of 1. The following conversion factors were used : levodopa controlled release preparations=0.77, bromocriptine=10, apomorphine=15, ropinirole=20, pramipexole=60, and pergolide=100

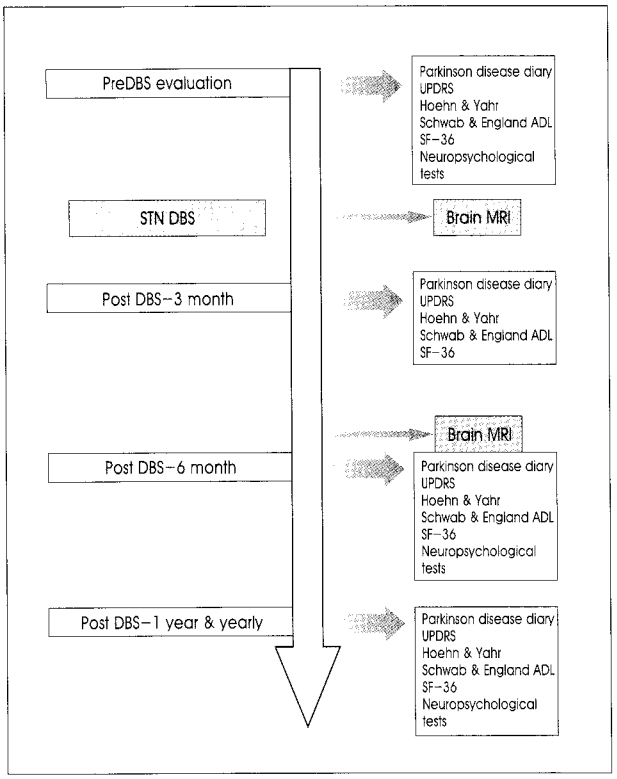

Fig. 1. The prospective protocol. Before determination of surgery, all surgical candidates are admitted to MUMD with a video recording by monitoring cameras for 3 days and 24 hours a day. During admission, patients are asked to fill out the PD diary every day. Neurological evaluations are performed using the Unified Parkinson Disease Rating Scale (UPDRS), Hoehn and Yahr Staging, and Schwab and England Activities of Daily Living (SEADL). These assessments are conducted separately when patients are off and on medications. The patients are supposed to be admitted to MUMD for 2 days at 3, 6, 12 months, and then yearly after surgery for evaluation with the same protocol including the Short Form-36 Health Survey (SF-36). The neuropsychological tests are also supposed to be evaluated before and at 6, 12 months, and then yearly after STN DBS. Scanning of MR images of the brain is supposed to be performed preoperatively and 6 months after surgery.

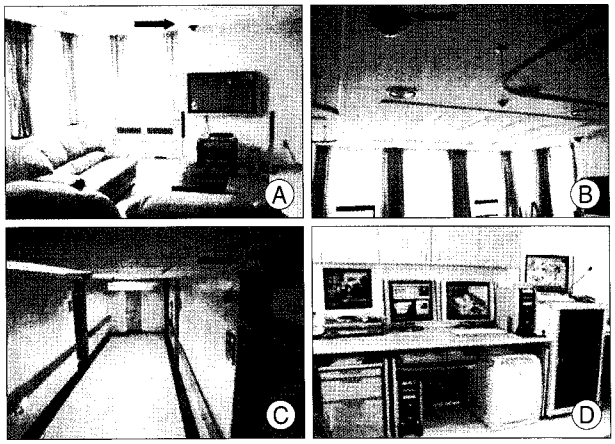

Fig. 2. The interior and the equipment. Monitoring cameras (arrows) are mounted on the ceiling of the patient's room (A, B) and corridor of ward (C) in order to more closely monitor the actual, whole-day-long clinical status of patients with Parkinson's disease. D shows a video recording/editing system in the monitoring room.

Prospective protocol

The protocol for the evaluation of patients with PD is summarized in Fig. 1. All surgical candidates were admitted over a period of 3 days to MUMD with 24-hour monitoring using cameras and a video recording/editing system (Fig. 2). The neurological evaluations were performed using the Unified Parkinson Disease Rating Scale (UPDRS), Hoehn and Yahr Staging, and Schwab and England Activities of Daily Living (SEADL). A treatment plan was determined for each patient according to the results of these thorough evaluations.

The levodopa equivalent daily dose (LEDD) was computed for each anti-parkinsonian medication by multiplying the total daily dosage of each drug by its potency relative to a standard levodopa preparation assigned the value of 1 as previously described[28].

The Short Form-36 Health Survey (SF-36) and neuropsychological tests were also evaluated before and after STN DBS.

Patient selection for STN DBS and their characteristics

The indication of STN DBS was advanced idiopathic PD with at least two cardinal features of parkinsonism (tremor, rigidity, and bradykinesia), a good response to levodopa, drug-induced side effects such as dyskinesia, hallucination, or motor fluctuation, and the unsatisfactory management of fluctuations with medication. Patients with severe cognitive impairment or dementia, ongoing psychiatric problems, an unsatisfactory general condition ; or an inability to comply with the study protocol, were all excluded. Approximately one fourth (n=42, 22%) of all candidates (n=194) with advanced PD admitted and evaluated by MUMD were selected for STN DBS on the basis of the above criteria. The clinical characteristics of these 42 patients are summarized in Table 1.

Surgical technique

In all cases, a stereotactic Leksell®-G frame (Elekta Instruments AB, Stockholm, Sweden) was mounted on the head of the patient under local anaesthesia. A 1.5T MRI scanner (Genesis Signa®, GE medical systems) was utilized for the preoperative planning. One patient with a cardiac pacemaker underwent a brain MRI with a temporary endovascular cardiac stimulating electrode. The STN was localized by a combination of MRI, microelectrode recording (MER), and stimulation technique as previously described[17]. A multi-channel parallel probe (four or five channels, so called "Ben Gun") for the MER and stimulation was utilized. The quadripolar chronic electrodes (DBS 3389, Medtronic) were indwelled under local anaesthesia and the IPGs were then implanted subcutaneously under general anaesthesia in a single operation. The patients underwent a 3D spiral stereotactic computed tomography (CT) scan (64-channel Brilliance CT, Philips, Eindhoven, Netherlands) with a 1 mm slice immediately after the DBS surgery.

Adjustment after STN DBS

All patients stopped using the previous anti-Parkinsonian medications after surgery and an examination of the effectiveness and side effects of the four contacts of the electrodes was initially performed using an N'vision® programmer (Medtronic) to select the best contact of the electrodes and electrical settings for chronic stimulation by the neurologist from day one after surgery. After turning on the minimal stimulation starting at the lowest level around 1.0 volts the next day after surgery, the medication was then optimized by attempting to gradually increase the medication to the demand for the best status of motor functions in harmony with the DBS programming via 24-hour monitoring in the MUMD. The patients were supposed to be admitted to MUMD for 2 days at 3, 6, 12 months, and then yearly after surgery for evaluation with the same protocol as used before surgery. The patients were not allowed to modify the settings of the DBS by themselves. Whenever the DBS parameter adjustment was necessary, the patient was supposed to be admitted to MUMD for a couple of days to receive an intensive 24-hour-monitoring. The bipolar stimulation was chosen in some cases rather than monopolar stimulation in cases of better responses.

Postoperative MRI after STN DBS

A 1.5T MRI of the brain (Genesis Signa®, GE medical systems) was performed at six months after STN DBS to evaluate the parenchymal changes of the brain and the exact location of the electrodes for all patients who signed the informed consent form except for one patient who had a cardiac pacemaker.

Statistical analysis

The data are presented as the means ± SD. We used the paired Student's t-test or the paired Wilcoxon signed-rank test to compare the baseline data with the follow-up data. The significance level was set at $p < 0.05$.

RESULTS

The clinical outcome

Forty-two patients with advanced PD were treated with STN DBS and three of them underwent repeated operation,

as described in complication. All patients were followed-up and evaluated at three and six months after operation, respectively. Thirty of the operations were performed using a four-channel MER probe and 12 operations were performed using a five-channel MER probe. The average distance between the MRI-guided target and MER-guided target was 2.2±1.2 mm (range; 0.0-6.0 mm) in the left STN and 2.4±1.0 mm (range; 0.0-5.5 mm) in the right STN. The average hospital stay was 14.6±6.3 days (range : 8-33 days).

STN stimulation much improved motor symptoms and the outcome parameters in comparison with the pre-operative status, as summarized in Table 2. The off-time total UPDRS scores improved from 68.4±19.9 before surgery to 44.6±14.4 ($p<0.001$) at three months and 46.8±18.6 ($p<0.001$) at six months after STN DBS. The off-time UPDRS-III motor scores improved from 39.3±14.8 before surgery to 23.7±10.1 ($p<0.001$) at three months and 23.6±12.4 ($p<0.001$) at six months after STN DBS. The on-time UPDRS-III motor scores im-proved from 20.1±11.3 before surgery to 15.8±8.6 ($p=0.022$) at six months after STN DBS. The off-time Hoehn & Yahr scores improved from 3.2±0.9 before surgery to 2.7±0.8 ($p<0.001$) at three months and 2.6±0.8 ($p<0.001$) at six months after STN DBS. The off-time SEADL scores improved from 50.0±20.9 before surgery to 68.9±21.2 ($p<0.001$) at three months and 66.4±20.1 ($p<0.001$) at six months after STN DBS. The dyskinesia disability scores improved from 2.6±1.1 before surgery to 0.7±1.2 ($p<0.001$) at three months and 0.6±1.2 ($p<0.001$) at six months after STN DBS. The LEDD also decreased postoperatively by about 50% from 790.4±375.7 mg/day to 324.1±345.0 mg/day at 2 weeks ($p<0.001$), 355.3±317.7 mg/day at 1 month ($p<0.001$), 359.4±303.9 mg/day at 2 months ($p<0.001$), 353.9±300.9 mg/day at 3 months ($p<0.001$), and 374.2±324.4 mg/day at 6 months ($p<0.001$) after STN stimulation (Fig. 3).

Considering the sub-score on part III of the UPDRS, tremor and rigidity were the most significantly improved motor symptoms following surgery (Table 3). The off-time tremor sub-scores improved from 7.1±5.1 before surgery to 1.5±1.8 ($p<0.001$) at three months and 1.3±2.2 ($p<0.001$) at six months after STN DBS. The on-time tremor sub-scores improved from 2.5±2.6 before surgery to 0.9±1.8 ($p=0.001$) at three months and 0.4±1.0 ($p<0.001$) at six months after STN DBS. The off-

Table 2. Surgical outcomes of 42 patients with Parkinson's disease after bilateral STN stimulation*

	Dopaminergic Medication	Stimulation	Baseline	3 months	6 months	p-value	
						3 months vs baseline	6 months vs baseline
Total	On	Off	32.4±16.9				
UPDRS	Off		68.4±19.9				
	On	On		30.9±14.6	29.7±12.9	p=0.620	p=0.252
	Off			44.6±14.4	46.8±18.6	p<0.001†	p<0.001†
UPDRS III	On	Off	20.1±11.3		28.8±14.9		p<0.001†
	Off		39.3±14.8		35.2±14.1		p=0.046†
	On	On		17.0±9.3	15.8±8.6	p=0.109	p=0.022†
	Off			23.7±10.1	23.6±12.4	p<0.001†	p<0.001†
H & Y	On	Off	2.4±0.7				
	Off		3.2±0.9				
	On	On		2.3±0.7	2.3±0.7	p=0.628	p=0.250
	Off			2.7±0.8	2.6±0.8	p<0.001†	p<0.001†
Schwab & England ADL	On	Off	78.2±16.6				
	Off		50.0±20.9				
	On	On		82.0±18.6	81.7±16.7	p=0.213	p=0.257
	Off			68.9±21.2	66.4±20.1	p<0.001†	p<0.001†
Dyskinesia diability			2.60	0.69	0.61	p<0.001†	p<0.001†
LEDD (mg/day)			790.4±375.7	353.9±300.9	374.2±324.4	p<0.001†	p<0.001†

The total scores of the UPDRS in the off-medication state were significantly improved postoperatively from the baseline value by 35% at three months and 32% at six months, respectively. However, the total scores of the UPDRS in the on-medication state were not significantly reduced. The outcome analyses of the scores on part III of the UPDRS (motor score) showed the same results as the total scores of the UPDRS in the off-stimulation state. However, the improvement in the on-stimulation state was only significant in the on-medication state. The scores of the Hoehn & Yahr stage and those of Schwab and England Activities of Daily Living (SEADL) also significantly improved from the baseline value primarily in the off-medication state during the short-term follow-up periods. Compared with the baseline values, the severity of the diability related to dyskinesia significantly decreased by 77%. The LEDD also decreased postoperatively by about 50% from 790.4±375.7 mg/day to 353.9±300.9 mg/day at 3 months ($p<0.001$), and 374.2±324.4 mg/day at 6 months ($p<0.001$) after STN stimulation. * Plus minus values are means±SD, †The asterisks indicate $p<0.05$ and statistical significance

time rigidity sub-scores improved from 8.0±3.3 before surgery to 4.0±3.2 ($p<0.001$) at three months and 4.2 ±3.9 ($p<0.001$) at six months after STN DBS. The off-time bradykinesia sub-scores improved from 12.8±6.1 before surgery to 8.9±5.5 ($p=0.002$) at three months and 8.9±5.8 ($p=0.004$) at six months after STN DBS. The off-time gait sub-scores improved from 1.9±0.8 before surgery to 1.4±0.8 ($p=0.003$) at three months and 1.4±0.8 ($p=0.017$) at six months after STN DBS, respectively. The off-time postural stability sub-scores improved from 1.8±0.9 before surgery to 1.3±0.9 ($p=0.003$) at three months and 1.2±0.9 ($p<0.001$) at six months after STN DBS. However, the speech sub-scores did not improve in both off-time and on-time at three and six months after bilateral STN DBS.

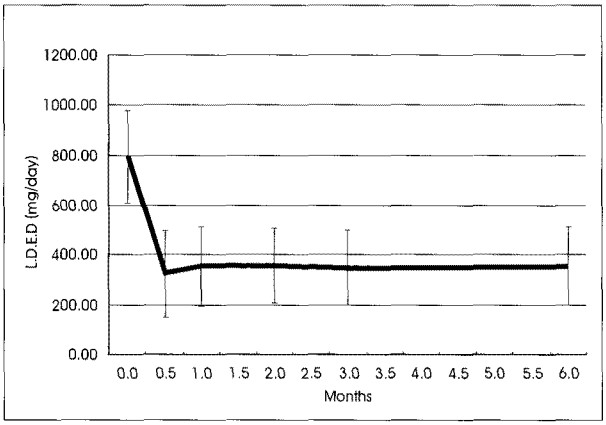

Fig. 3. L-dopa equivalent daily dose (LEDD) change before and after STN DBS in 42 patients with Parkinson's disease. The preoperative LEDD was 790.4±375.7 mg/day. The LEDD decreased postoperatively to 324.1±345.0 mg/day at 2 weeks ($p<0.001$), 355.3±317.7 mg/day at 1 month ($p<0.001$), 359.4±303.9 mg/day at 2 months ($p<0.001$), 353.9±300.9 mg/day at 3 months ($p<0.001$), and 374.2±324.4 mg/day at 6 months ($p<0.001$) after STN stimulation.

The scores of physical functioning, bodily pain, and general health among the eight scales of the SF-36 were significantly improved at three months after surgery (Table 4). The results of the neuropsychological tests performed in thirty-three patients showed that the score of Stroop test was aggravated from 1.86 to 2.21 ($p=0.019$) at six months (Table 5). Other tests such as TMT attention test, K-BNT

Table 3. Surgical outcome of each major motor symptom expressed in the mean UPDRS III scores in 42 patients with Parkinson's disease after bilateral STN stimulation†

	Dopaminergic Medication	Stimulation	Baseline	3 months	6 months	p-value	
						3 months vs baseline	6 months vs baseline
Speech	On	Off	1.3±0.7		1.5±0.6		p=0.300
	Off		1.7±0.6		1.6±0.6		p=0.593
	On	On		1.4±0.8	1.3±0.8	p=0.932	p=0.873
	Off			1.5±0.8	1.5±0.7	p=0.146	p=0.379
Tremor	On	Off	2.5±2.6		1.9±2.9		p=0.340
	Off		7.1±5.1		2.9±3.6		p<0.001*
	On	On		0.9±1.8	0.4±1.0	p=0.001†	p<0.001*
	Off			1.5±1.8	1.3±2.2	p<0.001†	p<0.001*
Rigidity	On	Off	4.2±3.1		5.4±4.4		p=0.179
	Off		8.0±3.3		6.4±4.1		p=0.092
	On	On		3.0±2.9	2.5±3.2	p=0.081	p=0.034*
	Off			4.0±3.2	4.2±3.9	p<0.001†	p<0.001*
Bradykinesia	On	Off	7.4±4.8		11.6±7.2		p=0.002*
	Off		12.8±6.1		13.7±7.3		p=0.410
	On	On		6.4±5.0	6.3±5.3	p=0.413	p=0.433
	Off			8.9±5.5	8.9±5.8	p=0.002†	p=0.004*
Gait	On	Off	0.8±0.7		1.6±1.1		p<0.001*
	Off		1.9±0.8		1.9±1.1		p=0.748
	On	On		0.8±0.6	1.0±0.7	p=0.668	p=0.083
	Off			1.4±0.8	1.4±0.8	p=0.003†	p=0.017*
Postural stability	On	Off	1.1±0.8		1.2±1.0		p=0.612
	Off		1.8±0.9		1.5±0.9		p=0.043*
	On	On		0.9±0.9	0.7±0.8	p=0.235	p=0.029*
	Off			1.3±0.9	1.2±0.9	p=0.003†	p<0.001*

The total scores of the UPDRS in the off-medication state were significantly improved postoperatively from the baseline value by 35% at three months and 32% at six months, respectively. However, the total scores of the UPDRS in the on medication state were not significantly reduced. *$p<0.05$ and statistical significance, †Plus-minus values are means±SD

language test, Rey-Kim memory test, sensory-motor coordinate test, frontal lobe function test such as fluency test and WCST, MMSE, and BDI were not changed significantly after surgery.

The mean body weight at six months after STN DBS was 59.9±8.5 kg (56.3±8.9 kg before surgery). The average body weight gain at six months after STN DBS was 3.6±3.4 kg ($p<0.001$).

Complications

A total of 13 patients (30.1%) suffered adverse effects after DBS surgery, including the mal-position of electrodes (Table 6). A small intracerebral hemorrhage (ICH) along the tract of electrodes was found in four patients. Immediate postoperative CT scans demonstrated small ICHs along the trajectory of the electrodes in four patients, three of whom were asymptomatic and one patient with transient dysarthria.

The 3D CT scan of one patient examined immediately after STN DBS demonstrated that an electrode targeted on the left STN was indwelled in the third ventricle, which might have been caused by technical error in aligning the AC-PC plane of MR images. The patient underwent re-operation two days after the initial surgery to reposition the left electrode.

Two other patients underwent re-operation to reposition the electrodes which were too medially located near or in the red nucleus. It was confirmed by the fused image of pre- and post-operative MRI taken at 6 months after STN DBS.

MRI of the brain after DBS

All patients, except for one with a cardiac pacemaker, underwent a brain MRI at six months after STN DBS and none of them experienced any adverse effects in performing MRIs. However, mal-positioned electrodes were detected by the brain MRIs of two patients, which were performed at less than six months after STN DBS

Table 4. Summary of the Short Form-36 Health Survey outcomes in 42 patients with Parkinson's disease after bilateral STN stimulation†

SF-36 scales	Baseline	3 months Scores	6 months	*p* value	
				3 months vs baseline	6 months vs baseline
Scales					
PF	32.0±22.0	46.0±24.9	44.1±24.2	$p=0.001$	$p=0.005$*
RP	15.0±23.2	23.8±30.7	21.7±30.9	$p=0.319$	$p=0.648$
BP	37.4±27.1	58.0±25.4	60.3±25.7	$p=0.003$*	$p=0.001$*
GH	42.1±19.6	55.0±22.1	50.9±21.9	$p=0.001$*	$p=0.030$*
VT	34.5±21.1	42.9±18.9	39.3±20.6	$p=0.026$	$p=0.089$
SF	42.1±26.3	99.6±54.4	53.7±20.0	$p=0.126$	$p=0.050$*
RE	17.5±31.1	52.6±28.2	24.6±37.7	$p=0.051$	$p=0.727$
MH	47.6±19.6	33.3±38.0	51.3±18.4	$p=0.182$	$p=0.486$
Summary scales					
PCS	689.6±339.5	945.6±419.7	902.8±388.9	$p=0.002$*	$p=0.012$*
MCS	531.2±244.9	657.9±266.6	588.1±266.9	$p=0.018$*	$p=0.194$

The scores of physical functioning, bodily pain, and general health among the eight scales of the SF-36 were significantly improved three months after surgery. Similar results were observed six months after surgery as were observed at three months after surgery in that the bodily pain was continuously and progressively improved. The postoperative physical component summary score significantly increased from the preoperative value. *$p<0.05$ and statistical significance, †Plus-minus values are means±SD. PF : Physical Functioning, RP : Role Physical, BP : Bodily Pain, GH : General Health, VT : Vitality, SF : Social Functioning, RE : Role Emotional, MH : Mental Health, PCS : Physical Component Summary, MCS : Mental Component Summary

Table 5. The results of the neuropsychological tests before and at six months after bilateral STN stimulation†

Newepsychological tests	Baseline	6 months	*p* value†
Attention	2.69±0.59	2.87±0.56	0.109
Language			
Ordinal scale	2.09±0.38	2.12±0.49	0.655
Total score	48.42±5.78	47.42±7.70	0.549
Memory	2.21±0.49	2.18±0.47	0.655
Sensory-Motor coordination			
Right	135.19±47.97	143.09±60.33	0.978
Left	151.85±73.62	153.00±48.81	0.489
Frontal lobe function			
Stroop	1.88±0.74	2.18±0.58	0.019*
Fluency	1.55±0.62	1.63±0.55	0.157
WCST			
Ordinal scale	2.31±0.69	2.53±0.57	0.071
Total score	40.65±8.20	39.54±7.08	0.572
MMSE			
Ordinal scale	2.22±0.42	2.36±0.49	0.102
Total score	26.96±1.93	26.67±2.23	0.450
BDI			
Ordinal scale	2.59±0.98	2.76±0.97	0.378
Total score	20.19±11.62	21.61±10.16	0.476

We used an ordinal scale (1-3 for MMSE, 1-4 for BDI and otherwise 1-5) to assess any improvement or decline in addition to the scores of the MMSE, BDI, and WCST. † Plus-minus values are means±SD. ‡The nonparametric Wilcoxon signed rank test was used and $p<0.05$ was considered to be statistically significant (*). WCST : Wisconsin card sorting test, MMSE: mini-mental status exam, BDI : Beck depression inventory. The results of a total of 33 patients who performed the neuropsychological tests before and after surgery were analyzed

Table 6. Complications of 42 patients with Parkinson's disease after bilateral STN stimulation

Complications		Number of patients	Percentage
ICH*	Symptomatic	1	2.4%
	Asymptomatic	3	7.1%
Transient abulia & confusion		1	2.4%
Transient dysarthria		1	2.4%
Transient hypophonia		1	2.4%
Transient restless leg syndrome		1	2.4%
Wound infection**		1	2.4%
Personality change***		1	2.4%
Malposition		3	7.1%
Total		13	30.9%

*A small intra-cerebral hemorrhage (ICH) along the tract of electrodes was found in four patients. Immediate postoperative CT scans demonstrated small ICHs along the trajectory of the electrodes in four patients, most of whom were asymptomatic except for one patient with transient dysarthria. **The patient suffered from a wound infection at the IPG site indwelled in the left subclavicular area. The infection was controlled with eight weeks of antibiotic therapy. ***The majority of the transient adverse effects after STN DBS disappeared within two to four weeks. However, one patient experienced a permanent personality change of a passive and dependent character after DBS surgery

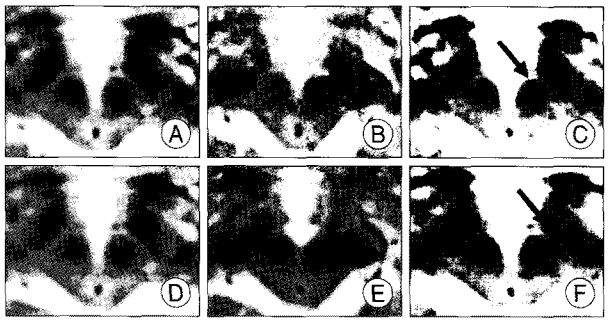

Fig. 4. MR images before and after STN DBS in a patient who underwent revision surgery. A 67-year-old male patient had undergone bilateral STN stimulation to alleviate the sufferings from drug-induced side effects and motor fluctuation following the 9-year use of dopaminergic drugs. However, it had resulted in no improvement of the symptoms in the right extremities with dysarthria and gait difficulty. Also, his MR images taken at 5 months after surgery demonstrated that the DBS electrodes were positioned off the STNs. He received a repeat surgery to reposition the left STN DBS electrode. The follow-up MR images in the middle column (B, E) are merged with the preoperative images in the left column (A, D). The fusion images in the right column (C, F) show the different locations (arrows) of the left STN DBS electrodes in the red nucleus (C) and in the subthalamic nucleus (F), respectively. The images of the upper row (A, B, C) were taken at 5 months after the first surgery and those of the lower row (D, E, F) were taken at 6 months after the revision surgery to reposition the left STN DBS electrode. The right sided symptoms of the patients as well as speech and gait difficulty were dramatically improved after the revision surgery.

because symptom improvement was less than expected after surgery. Their MRIs demonstrated that the DBS electrodes were positioned off the STNs. Both patients underwent re-operations and experienced good clinical improvements. Their MRIs per-formed at six months after the repeated surgeries demons-trated that the DBS electrodes were well positioned in the STNs (Fig. 4).

DISCUSSION

The National Health Insurance of Korea initially reimbursed the DBS in January 2005. Thereafter, many patients with advanced PD in Korea had better chances of being properly treated with DBS. MDC was launched in March 2005 as a specialized MUMD system with a 24-hour monitoring unit equipped with video cameras and a recording system to more accurately monitor the actual, whole-day-long clinical status of the patients with PD (Fig. 2).

The clinical outcomes after STN DBS in our 42 patients with advanced PD were comparable with those of the previous reports in many institutes. However, two things are noteworthy about our study in comparison with the other studies. First, the means of LEDD before and after surgery were much lower in our study than those reported in the previous literatures (Table 7). The mean LEDD of the patients was 790.4 ± 375.7 mg/day at baseline, and 353.9 ± 300.9 mg/day ($p < 0.001$) at three months and 374.2 ± 324.4 mg/day at six months ($p < 0.001$) after STN DBS. The mean LEDD of our patients was decreased by 60% of the baseline level at three and six months after STN DBS. Anti-parkinsonian medications were totally withdrawn at six months in nine (24.1%) of 42 patients. The mean LEDD in our study was one of the lowest results of the previous reports[6,11,12,14,16,19,20,28,31,34]. One of the many multi-factorial reasons for the use of about half of the LEDD used in other reports may be a strict dose readjustment following the early reduction of anti-Parkinsonian medications accompanied by the prolonged monitoring in MUMD. However, although the computation of the LEDD is a useful tool to summarize the total medication given to a patient, flexibility must be exercised when making comparisons because the LEDD is an artificial tool and the formulas for computing LEDD vary slightly in different reports[28].

Another noteworthy finding of this study is that the DBS was turned on at lowest level around 1.0 volt from the next day after surgery, which is different from the literature reports[6,11,12,14,16,19,20,28,31,34]. After turning on the minimal stimulation the next day after surgery, the medication was then optimized by attempting to gradually increase the medication to the demand for the best status of motor functions in harmony with the DBS programming. During the postoperative admission period (average : 9.7 ± 6.3 days, range : 3-29 days), antiparkinsonian medications were minimized and electrical stimulation was started with contact 1 from day 1 after surgery. Rough adjustment of the DBS parameters and medications were made until discharge. Further adjustment of the DBS parameters and medications

Table 7. The published results regarding the levodopa equivalent daily dose after STN DBS for advanced Parkinson's disease†

References		Pt No	Baseline (mg/day)	3 months* (mg/day)	6 months* (mg/day)	1 year* (mg/day)	3 years* (mg/day)	5 years* (mg/day)	No of quit medication**
The present study		42	790.4±375.7	353.9±300.9	374.2±324.4				9 (21.4%)
Godinho et al[12]	2006	28	1292.4±869		405±383.9				N.A.
Capecci et al[6]	2005	23	987±427			708±311	561±347		N.A.
Minguez et al[19]	2005	10	1394±500			1034±451			N.A.
Krack et al[14]	2003	49	1409±605			584±366	526±328	518±338	3 (6.1%)
Romito et al[28]	2003	33	1349.3±692.9	626.5±380.3	616.7±333.0	471.4±281.4			N.A.
Thobois et al[31]	2002	18	1045±435		360±377				6 (33.3%)
The DBS for PD	2001	96	1218.8±575		764.0±507				N.A.***
Study group[8]									
Volkmann et al[34]	2001	46	913±479		395±298	335±221			N.A.
Fraix et al[11]	2000	24	952±509	223±169		184±190			8 (33.3%)
Moro et al[20]	1999	7	1507.3±821.5	558.7±124.9	526.7±106.8	535.8±87.9			N.A.
Kumar et al[16]	1998	7	1612±518		967±515				N.A.

*Follow-up duration after surgery, **No of quit medication : number of patients whose antiparkinsonian drugs, including levodopa, were totally withdrawn until the last follow-up, ***not available, † Plus-minus values are means±SD

were done during a weekly outpatient visit until satisfactory. Systematic examination of the effectiveness and side effects of the four contacts of the electrodes was performed using an N'vision® programmer (Medtronic, Minneapolis, WI) to select the best contact of the electrodes and electrical settings for chronic stimulation by the neurologists in 4 weeks after surgery. Monopolar stimulation was preferred, and bipolar stimulation was chosen occasionally in cases of better responses.

This process usually took one month after STN stimulation surgery. This strategy can reduce the amount of anti-parkinsonian drugs and adjust the DBS parameters within a short period of time (Fig. 3). Usually, most patients would experience the microlesioning effect in this period after STN DBS, which could make the program-ming more difficult. However, the specialized 24-hour monitoring could make early reduction of anti-parkinsonian drugs feasible and practicable. Although there was no controlled study for this, it seems that the early adjustment of the DBS parameter in the off-medication state used in our protocol take less time to reach the equilibrium level between the anti-parkinsonian drug dose and DBS parameters for the best motor function. It also reduced the total consumption of anti-parkinsonian drugs for each patient until they seek the optimal drug dose for the best motor function. It also reduced the total consumption of anti-parkinsonian drugs for each patient until they seek the optimal drug dose for the best motor function with STN DBS. However, a multi-center controlled study will be necessary for the validation of this issue.

It is well known that the central trajectory of a Ben-Gun is not the optimal therapeutic trajectory in 30 to 35% of the STNs localized by MRI[4]. Bejjani et al. reported that MRI alone was not sufficient in their experience of 12 cases in which T2-weighted coronal images were used for targeting[1]. Zonenshayn and colleagues found that MRI targeting was the least accurate method with an average error of 2.6 mm[38]. Our experience supports their findings. In our patients, the average error was 2.2±1.2 mm (range; 0.0-6.0 mm) in the left STN and 2.4±1.0 mm (range; 0.0-5.5 mm) in the right side, respectively. However, the risk of bleeding does not seem to be more common in this study than the reports using macrostimulation alone for the targeting of the STN DBS. A small ICH less than 1 cm in diameter was detected in four (7.5%) of 53 procedures by 3D CT scan taken immediately after surgery. Transient dysarthria developed in just one of the patients with ICHs ; the other three patients were asymptomatic. Taken the total number of trajectories into consideration, the risk of bleeding was very low, 4 bleedings (1%) in 450 total trajectories (1%).

The safety of the MRI scan is another issue with those who were keeping DBS electrodes in their brains[13,22,36]. In 2000, Yamamoto et al. first reported a case of thalamic lesioning in a patient treated with a thalamic DBS after emergent cardioversion for the treatment of severe arrhythmia of the patient[36]. In 2005, Henderson et al. described a case of serious, permanent neurological injury secondary to a radiofrequency lesion produced by the heating of a DBS electrode associated with the MR image scanning of the lumbar spine in a patient with PD[13]. With those anec-dotal occurrences of severe adverse effects related with DBS in the brains, the FDA issued a warning about the possible significant side effects when brain MRIs were performed on patients with a DBS in their brain. The FDA public health notification titled "MRI-caused injuries in

patients with implanted neurological stimulators" issued on May 10th, 2005 was sent to neuroradiologists all over the world saying that the FDA had received several reports of serious injury, including coma and permanent neurological impairment, in patients with implanted neurological stimulators who underwent MRI procedures.

However, there have been many reports in which the careful following of the manufacturer's guidelines resulted in the safe performance of MRI examinations of patients with neurostimulation systems used for DBS[5,9,25,26,29,30,32,33,35,37]. The authors of this study followed the guidelines from the manufacturer and no one experienced any adverse effects in performing MRIs when taking the 1.5 Tesla brain MR images of 41 patients with STN DBS at six months after surgery. Furthermore, the analyses of the MRI scans after STN DBS allowed us to identify the mal-positioning of the electrodes off the STNs in two patients.

In many publications about the DBS in patients with advanced PD, only the different activities of various centers evaluated with a variety of protocols and by various neurosurgeons and neurologists in multi-center trials have been reported[3]. Thus, issues such as the mechanisms of action in DBS, the exact localization of STN DBS electrodes in the brain, their efficacy or adverse effects according to loci of STN DBS electrodes, and the possible neuro-protective effect of DBS remain under debate. A well-organized evaluation system with a carefully designed consistent protocol is mandatory for these fundamental questions to be answered. Despite the drawbacks of this study, such as the lack of information on the long-term outcome, the authors hope that this type of study will shed some positive light on the answers to those fundamental questions in the near future.

CONCLUSION

In this paper, the authors evaluated the short-term outcome of bilateral STN stimulation for patients with advanced PD evaluated in a 24-hour monitoring unit for movement disorder using a prospective protocol in a single institute. We found that evaluations in a 24-hour monitoring unit could make it possible to efficiently reduce the dose of anti-Parkinsonian medication to an optimal level with patients' comfort after surgery and improve the clinical symptoms in harmony with STN stimulation.

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