DEEP-BRAIN STIMULATION OF THE SUBTHALAMIC NUCLEUS OR THE PARS INTERNA OF THE GLOBUS PALLIDUS IN PARKINSON'S DISEASE

THE DEEP-BRAIN STIMULATION FOR PARKINSON'S DISEASE STUDY GROUP*

ABSTRACT

Background Increased neuronal activity in the subthalamic nucleus and the pars interna of the globus pallidus is thought to account for motor dysfunction in patients with Parkinson's disease. Although creating lesions in these structures improves motor function in monkeys with induced parkinsonism and patients with Parkinson's disease, such lesions are associated with neurologic deficits, particularly when they are created bilaterally. Deep-brain stimulation simulates the effects of a lesion without destroying brain tissue.

Methods We performed a prospective, double-blind, crossover study in patients with advanced Parkinson's disease, in whom electrodes were implanted in the subthalamic nucleus or pars interna of the globus pallidus and who then underwent bilateral high-frequency deep-brain stimulation. We compared scores on the motor portion of the Unified Parkinson's Disease Rating Scale when the stimulation was randomly assigned to be turned on or off. We performed unblinded evaluations of motor function preoperatively and one, three, and six months postoperatively.

Results Electrodes were implanted bilaterally in 96 patients in the subthalamic-nucleus group and 38 patients in the globus-pallidus group. Three months after the procedures were performed, double-blind, crossover evaluations demonstrated that stimulation of the subthalamic nucleus was associated with a median improvement in the motor score (as compared with no stimulation) of 49 percent, and stimulation of the pars interna of the globus pallidus with a median improvement of 37 percent ($P<0.001$ for both comparisons). Between the preoperative and six-month visits, the percentage of time during the day that patients had good mobility without involuntary movements increased from 27 percent to 74 percent ($P<0.001$) with subthalamic stimulation and from 28 percent to 64 percent ($P<0.001$) with pallidal stimulation. Adverse events included intracranial hemorrhage in seven patients and infection necessitating removal of the leads in two.

Conclusions Bilateral stimulation of the subthalamic nucleus or pars interna of the globus pallidus is associated with significant improvement in motor function in patients with Parkinson's disease whose condition cannot be further improved with medical therapy. (N Engl J Med 2001;345:956-63.)

LEVODOPA is the mainstay of treatment for Parkinson's disease.[1] However, long-term levodopa treatment is complicated by involuntary movements known as dyskinesia and motor fluctuations in which patients cycle between periods of good mobility ("on" periods) and impaired mobility ("off" periods).[2] These complications result in disability that cannot be satisfactorily controlled by medical therapy in the majority of patients. Advances in understanding of the pathophysiology of the basal ganglia have provided opportunities for new therapeutic strategies to manage these problems.[3-5] In animal models of Parkinson's disease, neuronal activity is increased in the subthalamic nucleus and pars interna of the globus pallidus,[6] and lesions of these structures result in marked improvement in motor function.[6-8] These findings have led to the development of surgical procedures for Parkinson's disease that target the subthalamic nucleus and pars interna of the globus pallidus.[9,10]

In patients with Parkinson's disease, the creation of lesions in the pars interna of the globus pallidus (pallidotomy) improves contralateral dyskinesia and provides moderate antiparkinsonian benefits.[11,12] However, pallidotomy necessitates making a destructive brain lesion and entails the risk of inducing neurologic deficits, particularly with bilateral procedures.[13] The creation of lesions in the subthalamic nucleus also provides benefits to patients,[14] but is associated with the risk of hemiballismus.[15] Accordingly, physicians have been reluctant to perform bilateral pallidotomy or subthalamotomy.[10] High-frequency deep-brain stimulation of specific brain targets simulates the effect of a lesion without deliberately damaging the brain.[16] Deep-brain stimulation of the thalamus has been shown to control tremor[17] but not other, more disabling, features of Parkinson's disease. Studies in small numbers of patients with Parkinson's disease suggest that stimulation of the subthalamic nucleus and pars interna of the globus pallidus can improve the full constellation of parkinsonian motor features.[18-22] We evaluated the results

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of bilateral pallidal or subthalamic stimulation in patients with advanced Parkinson's disease.

METHODS

We performed a six-month, prospective, multicenter trial of bilateral deep-brain stimulation of the subthalamic nucleus or pars interna of the globus pallidus in patients with advanced Parkinson's disease. The study included a double-blind, randomized, crossover evaluation of the immediate effects of stimulation three months after implantation of the electrodes; unblinded evaluations of motor function two weeks before and one, three, and six months after implantation; and assessments of motor status with the use of a home diary.

Patients

The ages of the patients ranged from 30 to 75 years. The criteria for inclusion were the presence of at least two cardinal features of parkinsonism (tremor, rigidity, and bradykinesia), a good response to levodopa, a minimal score of 30 points on the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS) when the patient has been without medication for approximately 12 hours (scores on this scale range from 0 to 108; higher values indicate greater severity of symptoms[23]), and motor complications that could not be controlled with pharmacologic therapy. The criteria for exclusion were major psychiatric illness, cognitive impairment, other substantial medical problems or laboratory abnormalities, presence of a cardiac pacemaker, and previous intracranial surgery. The protocol was approved by the institutional review board of each participating center. All patients gave written informed consent.

Surgical Technique

The choice of the target site was determined at each center according to the experience and preference of the investigator. The target was identified by a combination of neuroimaging, microelectrode recording, and stimulation techniques.[16-22] A permanent electrode (Medtronic model 3387 or 3389, Medtronic, Minneapolis) containing four contact sites was implanted with the patient under local anesthesia and was connected to a pulse generator (Medtronic model 7424) that was placed subcutaneously in the subclavicular area with the patient under general anesthesia. The procedure was repeated on the opposite side of the brain either at the same time or within three months. Postoperatively, adjustment of medication was permitted if parkinsonism worsened or adverse events occurred. Levodopa dose equivalents were calculated as follows: 100 mg of standard levodopa equals 133 mg of controlled-release levodopa equals 10 mg of bromocriptine equals 1 mg of pergolide.

Stimulation Settings

The pulse generator could be programmed with respect to electrode contact (four sites), polarity (monopolar or bipolar), frequency (up to 185 Hz), voltage (up to 10.5 V), and pulse width (up to 450 μsec). The stimulation settings were selected to maximize clinical benefit and minimize side effects. Adjustments could be performed at any time throughout the study.

Evaluations

Methods of evaluation included the UPDRS, which incorporates assessments of motor function and activities of daily living,[23] and a dyskinesia-rating scale.[24] The dyskinesia score has a range of 0 (no dyskinesia) to 4 (severe dyskinesia). The double-blind, crossover study was performed after both medication and stimulation had been discontinued overnight. The patients were randomly assigned to undergo motor assessments in one of two treatment sequences. In sequence 1, the first evaluation was performed after stimulation had remained off for two additional hours and the second was performed after stimulation had been turned on for two hours; in sequence 2, the order was reversed. The investigators and patients were unaware of whether stimulation had been on or off. Permuted-block randomization was used to ensure uniform assignment of treatments to patients within each participating center and within each target site of implantation.

Unblinded base-line assessments were performed in the off-medication state (after overnight withdrawal of antiparkinsonian medication) and in the on-medication state (when the patient had his or her best response to the morning dose of antiparkinsonian medication). Unblinded postoperative evaluations were performed sequentially in four conditions (off medication, without stimulation; off medication, with stimulation; on medication, without stimulation; on medication, with stimulation). Evaluations with stimulation were performed after the stimulator had been turned on for approximately 30 minutes. Within each center, all assessments were performed by the same investigator.

The patients completed a home diary documenting their motor status at 30-minute intervals during the two days before each visit. Before the beginning of the study, they were instructed in the identification of three motor states: poor mobility ("off"), good mobility without dyskinesia ("on" without dyskinesia), and good mobility with dyskinesia ("on" with dyskinesia). At the completion of the study, the patients and investigators assessed the global effect of therapy.

Statistical Analysis

The primary outcome measure was the difference between scores on the motor subscale of the UPDRS performed with or without stimulation in the double-blind crossover component of the study. The Wilcoxon rank-sum test[25] was used to assess treatment, period, and carryover effects. The analysis of carryover effects assessed whether the treatment intervention in the first evaluation influenced the results obtained in the second. The analysis of the period effect assessed whether there was a difference in the results of stimulation in the two sequences. Secondary end points included the effect of stimulation on the change between base line and six months in the UPDRS motor score in the off-medication and on-medication states; the number of hours per day during which patients had good mobility without dyskinesia; scores on subscales of the UPDRS (activities of daily living, tremor, rigidity, bradykinesia, gait, and postural stability), and levodopa dose equivalents.

The Wilcoxon signed-rank test[25] was used for paired comparisons. Repeated-measures analysis of variance[25] was used to predict motor scores on the basis of three independent variables: stimulation status, medication status, and time. Analysis of the primary end point was performed for all randomized patients. All data collected at follow-up visits were used in the analysis of secondary end points. All enrolled patients were included in the analysis of adverse events. All P values were two-tailed. No interim analyses were performed.

Medtronic sponsored the study and was responsible for data collection, monitoring, and statistical analysis. The company had no role in study design, interpretation of data, or preparation of the manuscript for publication.

RESULTS

The study was conducted at 18 centers between July 1995 and July 1999. A total of 143 patients were enrolled; 134 received bilateral implants in the subthalamic nucleus or the pars interna of the globus pallidus and were included in the efficacy analysis. Nine patients did not receive bilateral implants. Table 1 shows the characteristics of the patients at base line. Bilateral procedures were performed in a single session in 87.5 percent of patients with subthalamic implants and 68.4 percent of those with pallidal implants. Table 1 also shows the stimulation settings at the time of the last visit.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 134 PATIENTS WITH BILATERAL IMPLANTS AND STIMULATION SETTINGS AT THE LAST FOLLOW-UP VISIT.*

VARIABLE	SUBTHALAMIC NUCLEUS	PARS INTERNA OF THE GLOBUS PALLIDUS
Base-line characteristic		
No. of patients	96	38
Sex		
Male	60	27
Female	36	11
Age at time of surgery (yr)	59.0±9.6	55.7±9.8
Age at onset of illness (yr)	44.6±8.9	41.2±9.5
UPDRS motor score†		
Off medication	54.0±15.1	50.8±11.6
On medication	23.6±10.2	24.1±14.6
Dose of levodopa or equivalent (mg/day)‡	1218.8±575	1090.9±543
Motor fluctuations (% of patients)	98	100
Dyskinesia (% of patients)	95	97
Stimulation settings at last follow-up		
No. of patients	91	36
Mean time to follow-up visit (mo)	6	6
Monopolar (%)	79.1	50
Voltage		
Mean	3.0	3.2
Range	0.8–8.0	1.1–5.5
Pulse width (μsec)		
Mean	82	125
Range	60–450	60–400
Frequency (Hz)		
Mean	152	162
Range	90–185	80–185

*Plus–minus values are means ±SD.

†UPDRS denotes the Unified Parkinson's Disease Rating Scale. The motor score has a range of 0 to 108, with higher levels indicating greater severity. Off-medication evaluations were performed when the patient had taken no antiparkinsonian medications for 8 to 12 hours. On-medication evaluations were performed during periods of maximal clinical benefit after the regular dose of antiparkinsonian medication.

‡Doses of other antiparkinsonian medications were converted to levodopa equivalents, as described in the Methods section.

TABLE 2. UPDRS MOTOR SCORES FOR THE RANDOMIZED, DOUBLE-BLIND CROSSOVER STUDY.*

PERIOD	SEQUENCE OF STIMULATION			
	SUBTHALAMIC NUCLEUS		PARS INTERNA OF THE GLOBUS PALLIDUS	
	Off first, then on (n=51)	*On first, then off (n=40)*	*Off first, then on (n=11)*	*On first, then off (n=24)*
	motor score			
1	50±17	31±17†	44±16	34±16†
2	27±14†	52±17	28±13†	48±17

*Values are means ±SD. Values are from the double-blind crossover evaluation conducted at three months. "Off" indicates that the patient was not receiving deep-brain stimulation, and "on" that stimulation had been received for two hours.

†$P<0.001$ for the difference between scores with and without stimulation.

Deep-Brain Stimulation of the Subthalamic Nucleus

One hundred two patients were enrolled in the subthalamic-nucleus group. Electrodes were bilaterally implanted in 96 patients, and 91 participated in the double-blind crossover evaluation and completed six months of follow-up. Bilateral procedures were not performed in six patients because of complications of the first surgical procedure (intracranial hemorrhage in two, hemiparesis in one, confusion in one, lack of response in one, and improper lead placement in one). Five did not participate in the double-blind evaluation or the six-month follow-up evaluation (two patients had infected leads, and three withdrew consent).

In the double-blind crossover study, there was a significant treatment effect associated with stimulation ($P<0.001$) (Table 2); there were no significant carryover effects ($P=0.38$) or period effects ($P=0.47$). Thus, stimulation in the first evaluation did not influence the results obtained in the evaluation without stimulation. In addition, stimulation produced the same result regardless of the order in which the patients were evaluated. Stimulation was associated with a mean improvement of 43 percent and a median improvement of 49 percent in the UPDRS motor score in comparison with the evaluation performed without stimulation ($P<0.001$). Significant benefits were also observed with stimulation in both sequences. A median improvement of more than 25 percent was noted at 15 of the 16 centers that performed this procedure.

The results of the unblinded evaluations are provided in Table 3. In comparison with base line, stimulation in the off-medication state was associated with significant improvement in the UPDRS motor score at each visit. Smaller, but significant, benefits were also noted with stimulation in the on-medication state. Stimulation status was significantly associated with the motor score in a repeated-measures analysis of variance ($P<0.001$). Significant interaction effects between medication and stimulation were observed, suggesting that stimulation and medication act synergistically in predicting motor scores. Follow-up visits did not predict motor score ($P=0.58$), indicating that the beneficial effect of stimulation was stable over time.

Stimulation in the off-medication state was also associated with significant improvement in tremor, rigidity, bradykinesia, gait, postural stability, and activities of daily living (Table 4). Home-diary assessments of the percentage of time with good mobility and without dyskinesia during the waking day increased from 27 percent to 74 percent between base line and six months ($P<0.001$); this was paralleled by a decrease in the percentage of time with poor mobility, from 49 percent to 19 percent ($P<0.001$) (Fig. 1). The mean (±SD) dyskinesia score improved from 1.9±1.1 at base line to 0.8±0.8 at six months ($P<0.001$). Global assessments by physicians and patients noted severe dis-

TABLE 3. EFFECT OF STIMULATION AND MEDICATION ON UPDRS MOTOR SCORES AT UNBLINDED EVALUATIONS.*

SITE AND CONDITIONS	PREIMPLANTATION	1 MO	3 MO	6 MO	PERCENT CHANGE†
		motor score			
Subthalamic nucleus					
No. of patients	96	92	94	91	
Off medication					
Without stimulation	54.0±15.1	52.4±17.1	53.0±16.9	53.1±17.1	
With stimulation		29.6±15.5‡	28.4±13.2‡	25.7±14.1‡	51.30
On medication					
Without stimulation	23.6±10.2	29.9±16.6	31.6±17.9	31.2±18.8	
With stimulation		18.4±11.9‡	19.1±11.6‡	17.8±12.1‡	25.80
Pars interna of the globus pallidus					
No. of patients	38	38	36	36	
Off medication					
Without stimulation	50.8±11.6	46.9±15.5	46.1±14.4	49.7±14.0	
With stimulation		30.8±13.8‡	31.5±13.0‡	33.9±12.3‡	33.30
On medication					
Without stimulation	24.1±14.6	19.3±9.8	20.5±11.6	19.4±10.0	
With stimulation		16.2±10.4§	16.3±9.7§	16.5±9.5§	26.80

*Plus–minus values are means ±SD.

†The change is the median percentage improvement in paired comparisons between six-month and base-line evaluations.

‡$P<0.001$ for the comparisons with base line and with the corresponding evaluation without stimulation.

§$P=0.003$ for the comparisons with base line and with the corresponding evaluation without stimulation.

TABLE 4. EFFECT OF SUBTHALAMIC AND PALLIDAL STIMULATION ON UPDRS SUBSCORES.*

SITE OF STIMULATION AND SUBSCALE	OFF MEDICATION			ON MEDICATION		
	BASE LINE	6 MO	P VALUE	BASE LINE	6 MO	P VALUE
	score			score		
Subthalamic						
Activities of daily living (range, 0–52)	28.4±8.7	16.0±8.0	<0.001	11.2±6.5	10.2±6.5	0.93
Tremor (range, 0–28)	7.3±6.5	1.5±2.2	<0.001	1.6±2.6	0.7±1.7	<0.001
Rigidity (range, 0–20)	10.6±3.9	4.4±3.3	<0.001	4.5±2.8	3.0±3.2	<0.001
Bradykinesia (range, 0–32)	18.6±6.0	10.7±6.9	<0.001	9.5±4.6	7.7±6.2	<0.001
Gait (range, 0–4)	2.7±1.0	1.2±1.0	<0.001	1.0±0.8	0.7±0.8	0.006
Postural stability (range, 0–4)	2.4±1.1	1.2±0.9	<0.001	1.2±0.8	0.9±0.9	0.05
Pars interna of the globus pallidus						
Activities of daily living	27.9±7.4	17.9±8.4	<0.001	12.7±5.6	8.8±6.5	<0.001
Tremor	6.9±5.4	2.8±3.8	<0.001	2.0±3.3	0.3±0.7	<0.001
Rigidity	10.2±3.4	7.1±3.8	<0.001	4.6±4.6	3.6±3.9	0.44
Bradykinesia	18.0±5.0	13.3±6.6	<0.001	8.8±5.6	6.9±5.0	0.17
Gait	2.6±0.9	1.7±1.0	<0.001	1.2±1.0	0.8±0.7	0.44
Postural stability	2.2±1.0	1.4±1.1	0.02	1.4±0.9	0.7±0.8	<0.001

*Plus–minus values are means ±SD. Higher scores in the activities-of-daily-living scale represent better function. Higher scores in all other items represent worse function. Ranges of possible scores are given in parentheses.

ability at base line in 74 percent and 77 percent, respectively, as compared with 15 percent and 23 percent at six months. Daily levodopa dose equivalents were reduced from a mean of 1218.8±575 mg at base line to 764.0±507 mg at six months ($P<0.001$).

Deep-Brain Stimulation of the Pars Interna of the Globus Pallidus

Forty-one patients were enrolled; electrodes were bilaterally implanted in 38 patients, 35 participated in the double-blind evaluation, and 36 completed six months of follow-up. Bilateral procedures were not performed in three patients because of cerebral hemorrhage in two and intraoperative confusion in one. Three patients did not participate in the double-blind evaluation (two refused, and one withdrew from the study). Two did not complete six months of follow-up (one withdrew, and one died).

The double-blind crossover evaluation performed at three months demonstrated a significant treatment effect in favor of stimulation ($P<0.001$) (Table 2). There were no significant carryover effects ($P=0.40$) or period effects ($P=0.50$). Stimulation was associated with a mean improvement of 32 percent and a median improvement of 37 percent in the UPDRS motor score ($P<0.001$). Median improvement greater than 25 percent was observed at 9 of 10 centers. The benefit of stimulation was seen regardless of the sequence assignment.

The results of the unblinded evaluations over the course of the study are provided in Table 3. In comparison with base line, there was significant improvement in the UPDRS motor score at each visit with stimulation in the off-medication state ($P<0.001$). Smaller, but significant, benefits were also noted with stimulation in the on-medication state ($P=0.003$). Repeated-measures analysis of variance demonstrated that stimulation was significantly associated with improvement in the motor score ($P<0.001$). An interaction effect between medication and stimulation was observed ($P<0.001$), and the beneficial effect of stimulation was stable over time ($P=0.72$).

The effects of pallidal stimulation on activities of daily living and the cardinal features of Parkinson's dis-

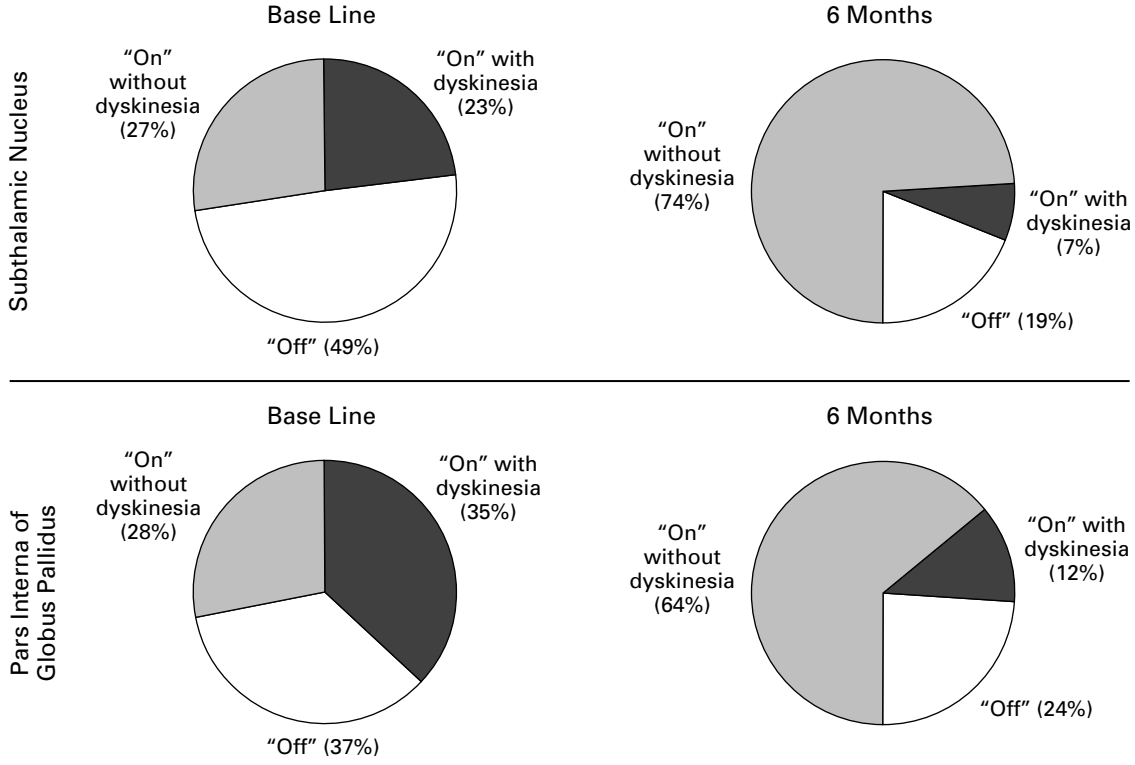

Figure 1. The Mean Percentage of Time during Waking Hours with Poor Mobility (the "Off" State), Good Mobility with Dyskinesia (the "On" State with Dyskinesia), and Good Mobility without Dyskinesia (the "On" State without Dyskinesia) at Base Line and Six Months after the Implantation of Electrodes for Bilateral Stimulation of Either the Subthalamic Nucleus or the Pars Interna of the Globus Pallidus.

The percentage of time in the "on" state without dyskinesia increased from 27 percent to 74 percent with bilateral stimulation of the subthalamic nucleus and from 28 percent to 64 percent with bilateral stimulation of the pars interna of the globus pallidus ($P<0.001$ for both comparisons). In addition, stimulation during "off" periods induced improvements in motor scores approximating those induced by levodopa.

ease are shown in Table 4. Significant benefits were observed, particularly in the off-medication state. Home-diary assessments indicated that between base line and six months, the percentage of time with good mobility and without dyskinesia during the waking day increased from 28 percent to 64 percent ($P<0.001$); the percentage of time with poor mobility was correspondingly reduced from 37 percent to 24 percent ($P=0.01$) (Fig. 1). The dyskinesia score improved from a mean of 2.1 ± 1.5 at base line to 0.7 ± 0.8 at six months ($P<0.01$). Physician and patient global estimates of severe disability improved from 76 percent and 82 percent, respectively, at base line to 11 percent and 14 percent at six months. The mean daily dose in levodopa equivalents was unchanged between base line (1090.9 ± 543 mg) and six months (1120 ± 537 mg).

Adverse Events

All serious or severe adverse events attributed to the intervention or affecting more than one patient are listed in Table 5. Intracranial hemorrhage occurred in seven patients (subcortical in five, subarachnoid in one, and within the subthalamic nucleus in one), four of whom required surgical decompression. Six patients had neurologic deficits associated with the hemorrhage, and four of these had persistent dysfunction (including hemiparesis, aphasia, and cognitive dysfunction). The number of microelectrode passes used to determine target location correlated with the risk of hemorrhage. Patients without hemorrhage had a mean of 2.9 ± 1.8 passes, as compared with 4.1 ± 2.0 among those who had hemorrhage ($P=0.05$). Four patients had seizures, two of which occurred in patients who had a cerebral hemorrhage. In all instances, seizures were able to be controlled with anticonvulsant medication. The device was explanted because of infection in two patients. Stimulation was frequently associated with muscle twitch and paresthesia, but these were typically transient and disappeared with adjustment of the stimulator settings. Five patients had stimulation-induced dyskinesia; in one patient the dyskinesia was severe but resolved with stimulator adjustment. One patient died of esophageal carcinoma.

TABLE 5. ADVERSE EVENTS ASSOCIATED WITH SUBTHALAMIC AND PALLIDAL STIMULATION.*

TYPE OF ADVERSE EVENT	SUBTHALAMIC NUCLEUS (N=102)	PARS INTERNA OF THE GLOBUS PALLIDUS (N=41)
	number	
Related to procedure		
Intracranial hemorrhage	3	4
Hemiparesis secondary to hemorrhage	3	3
Seizures	3	1
Infection	4	0
Improper lead placement	2	0
Brachial plexus injury	1	0
Confusion	1	0
Dysarthria	0	1
Paralysis (nonhemorrhagic)	1	0
Pulmonary embolus	1	0
Related to device		
Migration	3	2
Infection	3	1
Lead break	1	1
Seroma	1	1
Erosion	1	0
Abnormal healing	1	0
Intermittent function	1	0
Related to stimulation		
Dyskinesia	2	3
Diplopia	2	0
Dystonia	0	2
Abdominal pain	0	1
Accidental injury	1	0
Dysarthria	1	0
Headache	1	0
Paresthesia	1	0

*Some patients had more than one adverse effect.

DISCUSSION

We conducted a six-month, multicenter study of patients with advanced Parkinson's disease who underwent bilateral deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus. A double-blind, crossover evaluation demonstrated that stimulation of either target improved motor function in the off-medication state. Although initiation of stimulation was associated with transient symptoms in some patients, we do not believe that this influenced the blinded assessment, since neither the patients nor the investigators were certain of whether stimulation was being given at the time.

Unblinded evaluations showed that both subthalamic stimulation and pallidal stimulation were associated with improvement in motor score in the off-medication state. Benefits were observed with respect to total motor score, dyskinesia, activities of daily living, and each of the cardinal features of Parkinson's disease. Home-diary assessments indicated that patients in both groups had a significant increase in the percentage of "on" time without dyskinesia and a significant decrease in the percentage of "off" time. Furthermore, with stimulation, UPDRS motor scores during "off" periods were significantly improved and approximated motor scores during "on" periods induced by medical therapy. Thus, "off" periods were reduced in both frequency and severity, with the result that disability was markedly attenuated. This decrease was reflected in the global evaluation scores of both physicians and patients.

Stimulation in the on-medication state resulted in less pronounced but still significant clinical improvement, suggesting the possibility of synergism between subthalamic or pallidal stimulation and dopaminergic drugs. Such an effect has not been reported with other surgical therapies.[11,12,26,27] Dyskinesias were reduced in both groups. A reduction in levodopa dose equivalents may have contributed to this effect in pa-

tients treated with stimulation of the subthalamic nucleus. However, this would not account for the reduction in dyskinesia in patients who were receiving pallidal stimulation and in whom the levodopa dose equivalent was not reduced. Alternatively, high-frequency stimulation might have disrupted abnormal neuronal firing patterns in the subthalamic nucleus or the pars interna of the globus pallidus that are responsible for dyskinesia.[28] Our results are similar to those reported in other trials of subthalamic[18,19] and pallidal[20-22] stimulation that involved smaller numbers of patients.

There were seven cases of intracranial hemorrhage in 143 patients who underwent 277 stereotactic procedures. Two patients had infections necessitating removal of the electrodes. The remainder of the complications did not lead to serious morbidity or death. Four patients had persistent neurologic deficits (2.8 percent of patients and 1.4 percent of surgical procedures). This rate is less than that reported with other bilateral surgical procedures for Parkinson's disease.[11,13,29-31] There is controversy as to whether the benefit of microelectrode recordings used to facilitate target localization is offset by the risk of additional adverse events.[26,32,33] Our study suggests that increased numbers of microelectrode passes were associated with an increased risk of intracranial bleeding.

The mechanism of action of deep-brain stimulation remains to be defined.[34] Possible mechanisms include depolarization blockade, release of local inhibitory neurotransmitters, antidromic activation of inhibitory neurons, and jamming of abnormal neuronal firing patterns. By whatever mechanism, stimulation mirrors the effects of a destructive lesion.

In conclusion, bilateral stimulation of the subthalamic nucleus or pars interna of the globus pallidus provides significant motor benefits for patients with advanced Parkinson's disease, while reducing dyskinesia and motor fluctuations. Although we did not conduct a direct comparison, these benefits are of greater magnitude than has been achieved with thalamotomy,[31] unilateral pallidotomy,[11,12,30,35] thalamic stimulation,[17,36] or fetal nigral transplantation.[37,38] Serious adverse events appear to be less frequent with bilateral stimulation than with bilateral ablative procedures.[13,31] Patients were not randomly assigned to a target site of implantation, and the study was therefore not designed to compare subthalamic and pallidal stimulation. Nonetheless, subthalamic stimulation appears to be associated with a greater benefit and permitted a reduction in the consumption of levodopa or its equivalents. These observations suggest that stimulation of the subthalamic nucleus might be superior to pallidal stimulation, but further studies are required to determine whether one target is preferable to the other.

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APPENDIX

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