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Long-term evaluation of deep brain stimulation of the thalamus

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Object. The effects of thalamic deep brain stimulation (DBS) on essential tremor (ET) and Parkinson disease (PD) have been well documented, but there is a paucity of long-term data. The aim of this study was to evaluate the long-term safety and efficacy of DBS of the ventralis intermedius nucleus (VIM) of the thalamus for PD and ET.

Methods. Thirty-eight of 45 patients enrolled at five sites completed a 5-year follow-up study. There were 26 patients with ET and 19 with PD undergoing 29 unilateral (18 ET/11 PD) and 16 bilateral (eight ET/eight PD) procedures. Patients with ET were evaluated using the Tremor Rating Scale, and patients with PD were evaluated using the Unified Parkinson's Disease Rating Scale. The mean age of patients with ET was 70.2 years and 66.3 years in patients with PD. Unilaterally implanted patients with ET had a 75% improvement of the targeted hand tremor; those with bilateral implants had a 65% improvement in the left hand and 86% in the right compared with baseline. Parkinsonian patients with unilateral implants had an 85% improvement in the targeted hand tremor and those with bilateral implants had a 100% improvement in the left hand and 90% improvement in the right. Common DBS-related adverse events in patients receiving unilateral implants were paresthesia (45%) and pain (41%), and in patients receiving implants bilaterally dysarthria (75%) and balance difficulties (56%) occurred. Device-related surgical revisions other than IPG replacements occurred in 12 (27%) of the 45 patients.

Conclusions. Thalamic stimulation is safe and effective for the long-term management of essential and parkinsonian tremors. Bilateral stimulation can cause dysarthria and incoordination and should be used cautiously.

KEY WORDS • essential tremor • Parkinson disease • deep brain stimulation • thalamic stimulation

IN 1997, authors of a multicenter trial reported that in patients with disabling medication-resistant tremor attributable to either ET or PD, DBS of the thalamic VIM significantly improved tremor for as long as 1 year postsurgery.[5] These data led to the approval of Activa Tremor Control Therapy in the US and other countries. Although several other researchers have reported short-term improvement of tremor through DBS of the thalamus,[1,2,7–9] relatively few have evaluated long-term tremor control.[6,10,11] The current prospective multicenter study was conducted in the US at specific centers that had participated in the previously mentioned multicenter study (University of Kansas Medical Center, Baylor College of Medicine, Beth Israel Deaconess Medical Center, the Ohio State University, and University of South Florida).[5] The primary aim of our study was the evaluation of the long-term safety and efficacy of DBS of the thalamus for upper-extremity tremor in patients with ET or PD.

Abbreviations used in this paper: AC = anterior commissure; ADL = activities of daily living; DBS = deep brain stimulation; ET = essential tremor; IPG = implantable pulse generator; PC = posterior commissure; PD = Parkinson disease; TRS = Tremor Rating Scale; UPDRS = Unified Parkinson's Disease Rating Scale; VIM = ventralis intermedius nucleus.

Clinical Material and Methods

Inclusion criteria were as follows: 1) a diagnosis of ET or PD; 2) DBS of the thalamic VIM; 3) participation in the 1997 tremor control study with initial surgery occurring between 1993 and 1997; and 4) willingness to sign an informed consent form and to return for as many as five annual follow-up visits at the original investigative site. The protocol was approved by each institutional review board, and all patients provided written informed consent prior to study participation.

Surgical Procedure

Details of the surgical procedure have been described in a previous publication.[6] In brief, a stereotactic head frame (Cosman-Roberts-Wells; Radionics, Inc., Burlington, MA or Leksell; Elekta, Norcross, GA) was placed once a local anesthetic had been applied. Targeting was performed using either computerized tomography or magnetic resonance imaging. In cases of computerized tomography, a scan was obtained with the gantry angled either in or parallel to the AC–PC plane. Cuts were made at 1.5-mm intervals through the region of the thalamus. Location of the VIM was based on the AC–PC length divided by 12 and multiplied by 2.5 to attain the distance from the PC. The lateral coordinate was the sum of one half of the third ventricle's width plus 11.5 mm. The initial target depth was the AC–PC plane. For image targeting, 1-mm-thick slices through the thalamus were used to obtain coordinates for the AC and PC. The initial target was selected at the ventral border of the VIM based on a stereotactic atlas of the thalamus 15 mm from the midline; the atlas map was enlarged or shrunk in proportion to the patient's intercommissural distance. A bur hole was placed anterior to the coronal suture, 2.5 cm from the midline. Microelectrode recording and stimulation techniques were used to refine the target position. Once an optimal position was selected, macrostimulation was performed; if no side effects other than transitory paresthesias in the arm and face occurred, the DBS electrode (3387; Medtronic, Inc., Minneapolis, MN) was implanted. During the same surgical session, the IPG (7424; Itrel II, Medtronic, Inc.) was implanted and connected (7495; Medtronic, Inc.) to the DBS lead while the patient was in a state of general anesthesia.

Clinical Evaluation

Evaluations were based on the Fahn-Tolosa-Marin TRS[4] in patients with ET and on the UPDRS, Schwab and England ADL scale, and Hoehn and Yahr staging in patients with PD.[3] For each patient, rating scale subscores as well as targeted tremor scores, which represent the most severe tremor (that is, resting, postural, or kinetic), were analyzed. These scales were applied annually for 5 years from the date of the initial implant. Patients were enrolled in the study during the anniversary month of the initial implant ± 3 months. The number of evaluations that each patient underwent depended on the anniversary of the initial implant and when the patient entered the study. For example, if a patient entered the study after the 3-year anniversary of the initial implant, the patient would have undergone only two annual evaluations at Years 4 and 5.

In patients with ET, the TRS was completed at each annual follow-up visit. If a patient presented to the clinic in the stimulation-on condition, the stimulator was turned off and the TRS was completed 30 minutes thereafter. The stimulator was reprogrammed if clinically indicated in an attempt to deliver maximal benefit, and the motor section of the TRS (Items 1–14) was repeated in the stimulation-on state. In patients with PD, the UPDRS motor scores were evaluated in the stimulation-off state. Stimulators were then reprogrammed if necessary, and the patient was reevaluated using the complete UPDRS in the stimulation-on state. Medications were not controlled in this study. Adverse events related to the therapy, surgical procedure, and the DBS system were noted. In addition, stimulation parameters were recorded at the annual visits.

Statistical Analysis

Baseline follow-up tremor scores were evaluated using Wilcoxon signed-rank comparisons only in patients who had completed data for both time points. Patient tremor scores while in the stimulation-on condition were compared with those obtained in the stimulation-off state and also with baseline tremor scores. In addition, follow-up ADL scores were compared with baseline scores. Data were analyzed separately by disease but were pooled across centers. A probability value less than 0.05 was considered statistically significant. Data are presented as the means ± standard deviations.

Results

Forty-five patients at five sites were enrolled in the study. Twenty-six patients with ET, including 20 men (76.9%) and six women (23.1%), had a mean age of 70.2 ± 5.1 years (range 57–78 years). Nineteen patients with parkinsonian tremor had a mean age of 66.3 ± 9.9 years (range 38–78 years) including 17 men (89.5%) and two women (10.5%). Twenty-nine patients (18 with ET and 11 with PD) underwent unilateral implantation and 16 (eight with ET and eight with PD) underwent bilateral implantation. Of the 45 original patients, one was lost to follow up after a device-related loss of effect, three withdrew from the study (one due to stroke and two for unspecified reasons), one underwent explantation of the IPG during the 3-year follow-up period due to loss of effect, and two died of conditions unrelated to the DBS system before the 5-year follow-up visit (one due to congestive heart failure and one due to aspiration pneumonia caused by PD).

The remaining 38 patients (23 with ET and 15 with PD) completed at least part of the 5-year follow-up evaluation. The mean age of the patients with ET who completed the study was 70.6 ± 5.3 years (range 57–78 years) and included 17 men (73.9%) and six women (26.1%). The mean age of the patients with PD who completed the study was 63.7 ± 9.6 years (range 38–75 years) and included 13 men (86.7%) and two women (13.3%). Overall, 26 unilaterally implanted and 12 bilaterally implanted patients completed at least part of the 5-year follow-up evaluation.

Patients With ET

Unilateral Stimulation. Eighteen patients with ET had undergone unilateral implantation, although only 16 were available for the 5-year follow-up study. Investigator global ratings indicated that 13 patients experienced improvement compared with their baseline status and three had no improvement compared with baseline. According to patient global assessments, 15 patients experienced improvement compared with their baseline status and one patient's condition was unchanged. There was a 46% improvement in the mean motor tremor scores (TRS Items 1–10) in the stimulation-on state at 5 years postsurgery compared with baseline scores (Table 1). Similarly, there was a 51% improvement in ADLs (TRS Items 15–21), a 57% improvement in the mean drawing scores (TRS Items 11–13), and a 44% improvement in the mean pouring scores (TRS Item 14). The mean improvement in targeted (postural or kinetic) hand tremor was 75% compared with baseline. In the 16 patients who completed the 5-year evaluation there was a 75% improvement in targeted tremor when the mean stimulation-off scores were compared with the mean stimulation-on scores (Fig. 1).

Bilateral Stimulation. There were eight patients with ET who had undergone bilateral thalamic implantation, although only seven completed at least part of the 5-year fol-

TABLE 1

*Mean motor tremor scores in patients receiving unilateral or bilateral thalamic stimulation for ET**

Variable	Baseline	5-Yr FU Stim Off	5-Yr FU Stim On
unilat stim			
no. of patients	15	15	15
mean motor tremor score	21.5 ± 6.7	21.7 ± 6.9	11.7 ± 5.0
p value, compared w/ baseline		0.65	<0.01
p value, stim off compared w/ stim on		<0.01	
bilat stim			
no. of patients	7	7	7
mean motor tremor score	29.0 ± 7.7	21.3 ± 6.6	6.4 ± 2.4
p value, compared to baseline		0.02	0.02
p value, stim off compared w/ stim on		0.02	
combined groups			
no. of patients	22	22	22
mean motor tremor score	23.9 ± 7.8	21.6 ± 6.7	10.0 ± 4.9
p value, compared w/ baseline		0.21	<0.01
p value, stim off compared w/ stim on		<0.01	

* Motor tremor scores are based on the Fahn-Tolosa-Marín TRS, Items 1 to 10, for a possible score of up to 84. Results are based on Wilcoxon signed-rank comparisons of 5-year and baseline scores only in patients who had complete data for both time points. Mean values are presented as the means ± standard deviations. Abbreviations: FU = follow up; stim = stimulation.

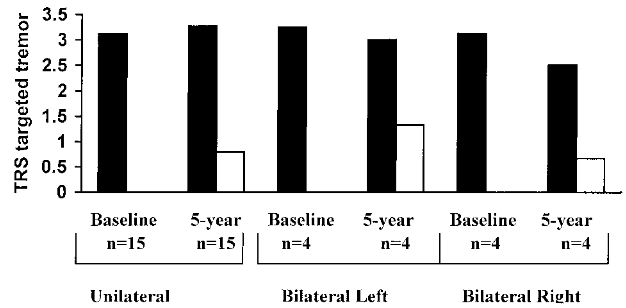

FIG. 1. Bar graph demonstrating mean tremor scores in patients with ET who received unilateral or bilateral thalamic stimulation. Results reflect targeted (postural or kinetic) tremor in the targeted limb (TRS score range 0–4). Five-year and baseline results are presented only for patients who had complete data at both time points. *Black bars* represent stimulation-off scores; *white bars* represent stimulation-on scores. N = number of patients.

low-up evaluation. Global ratings by investigators (seven reports) and patients (six reports) indicated that all patients improved compared with baseline status. There was a 78% improvement in the mean motor tremor scores (TRS Items 1–10) with stimulation on at 5 years compared with baseline (Table 1). Similarly, there was a 36% improvement in the mean ADL scores (TRS Items 15–21); a 35% improvement in the mean left-handed drawing scores and a 40% improvement in the right-handed scores (TRS Items 11–13); a 36% improvement in the mean left-handed pouring scores and a 57% improvement in the right-handed scores (TRS Item 14). There was a 65% improvement in the left-limb targeted tremor and an 86% improvement in the right-limb targeted tremor compared with baseline tremor. When the 5-year stimulation-off scores were compared with the stimulation-on scores, we noted a 58% improvement in the left limb tremor and a 81% improvement in the right limb tremor (Fig. 1).

Table 2 displays individual tremor scores at baseline and at 5 years postimplantation or the last follow-up visit in all 26 patients with ET. Analysis of these data indicated that 24 of 26 patients with ET had reduced tremor in the stimulation-on condition at the 5-year or last follow-up evaluation compared with baseline. Only one patient experienced a mild increase in tremor at 5 years compared with baseline. One patient exhibited no change in tremor compared with baseline at the 3-year follow up, and thus the stimulator was explanted. All 26 patients had improvement in tremor at 5 years posttreatment or by the last follow-up evaluation in the stimulation-on state compared with the stimulation-off state.

Stimulation Parameters. Among patients with ET, stimulator settings for unilateral and bilateral implants remained stable at the 5-year follow up compared with the 1st year settings. At the 5-year follow-up examination in patients with ET, the unilaterally implanted device was set at a mean amplitude of 3.6 V, pulse width of 111 μsec, and rate of 158 Hz; 19% of these patients received monopolar stimulation. In patients with a bilaterally implanted device, the first side had a mean amplitude of 3.6 V, pulse width of 111 μsec, and rate of 155 Hz, with all patients receiving bipolar stimulation; the second side had a mean amplitude of 3.2 V, pulse width of 129 μsec, and rate of 153 Hz, with all patients receiving bipolar stimulation. The stimulation amplitudes at 3 months postimplantation and at the 5-year or last follow-up evaluation in each of the 26 patients with ET are shown in Table 2. Amplitude was increased by at least 1 V in eight patients, remained relatively unchanged (< 1 V) in 16 patients, and decreased by at least 1 V in two patients.

Patients With PD

Unilateral Stimulation. Of 11 patients with PD who received unilateral stimulation, 10 completed the 5-year follow-up assessment. At 5 years postsurgery, subjective global assessments were available in nine patients; six rated their condition as improved and three as unchanged compared with baseline. Investigator global assessments were available in 10 patients, with improvement in three, no change in five, and a worse condition in two. There was no significant change in the UPDRS motor, bradykinesia, or rigidity scores over the 5-year period, compared with baseline (Table 3). There was also no change in the UPDRS ADL scores compared with baseline. Two patients reported reduced duration of dyskinesia, four reported no change, and one reported prolonged duration of dyskinesia compared with baseline. Four patients reported improvement in the amount of time spent in the medication-off state, two reported no change, and one patient reported decreased time in the medication-off state at 5 years postsurgery. The mean Hoehn and Yahr scores worsened from 2.3 to 2.9 and the Schwab and England percentages worsened from 74 to 66%. Improvement in the targeted limb tremor was 85% compared with baseline tremor. In the nine patients who underwent the 5-year evaluation and had complete tremor data, there was an 82% improvement in the targeted limb tremor when the stimulation-off scores were compared with the stimulation-on scores (Fig. 2).

Bilateral Stimulation. There were eight patients with par-

TABLE 2

Changes in tremor score and IPG amplitude in 26 patients with ET

Case No.	Stim Type	Tremor Score				IPG Amplitude†	
		Baseline	5-Yr Stim Off	5-Yr Stim On	% Decrease*	3 Mos Postop	5-Yr FU
1	unilat	29	26	11	58	3.7	4.9
2	bilat	26	22	6	73	3.5	4.7
3	unilat	28	19	11	42	2.0	2.0
4	unilat	19	30	13	57	2.9	2.5
5	unilat	20	24	13	46	3.7	3.8
6	unilat	23	25	16	36	3.8	5.0
7	unilat	21	18	7	61	3.2	2.8
8	unilat	24	17	9	47	3.1	2.5
9	unilat	36	39	21	46	3.5	3.0
10	bilat	29	25	6	76	4.1	2.6
11	bilat	20	8	6	25	3.6	3.8
12‡	unilat	8	12	7	42	2.2	2.0
13‡	bilat	20	24	9	63	3.5	3.5
14	unilat	15	11	7	36	4.1	3.8
15	unilat	9	15	5	67	3.5	3.5
16	unilat	13	20	15	25	3.0	5.0
17	unilat	27	31§	20§	35	3.5	1.4
18	unilat	17	19	6	68	2.8	3.6
19	bilat	42	25	3	88	2.2	4.0
20‡	unilat	26	31	26	16	2.2	3.5‖
21	unilat	23	16	12	25	4.3	4.5
22	unilat	25	26	21	19	3.5	4.0
23	bilat	35	28	11	61	4.1	4.3
24	bilat	21	18	6	67	3.0	3.7
25	bilat	30	23	7	70	2.1	2.2
26	unilat	20	21	8	62	3.9	5.9

* Stimulation-off scores minus stimulation-on scores.
† In patients receiving bilateral stimulation, amplitude refers only to the first implanted side.
‡ Patient did not have 5-year data; therefore, 3-year data were used.
§ Patient did not have 5-year data; therefore, 4-year data were used.
‖ Patient did not have 5-year data; therefore, 1-year data were used.

kinsonian tremor who had undergone bilateral thalamic implantation, and five of these completed the 5-year evaluation. At 5 years postsurgery, subjective global assessments were available in all five patients: two rated their condition as improved and three as unchanged, compared with baseline. Investigator global assessments were also available in all five patients: improvement was reported in one patient, no change in three, and worsening in one. There was no significant change in the UPDRS motor, bradykinesia, or rigidity scores over the 5-year period compared with baseline (Table 3). The UPDRS ADL scores worsened from 15.4 to 19.8. One patient reported decreased duration of dyskinesia, and three patients reported no change in the duration of dyskinesia. At 5 years postsurgery, one patient reported an increase in the amount of time spent in the medication-off state, and two patients reported decreased time spent in the off state. The mean Hoehn and Yahr stages worsened from 2.2 to 3.1 and the Schwab and England percentages worsened from 80 to 68%. In the five patients who underwent the 5-year evaluation, there was a 100% improvement in left limb tremor and a 90% improvement in right limb tremor, compared with baseline tremor scores. When the 5-year stimulation-off scores were compared with stimulation-on scores, there was a 100% improvement in left limb tremor and a 92% improvement in the right limb tremor scores (Fig. 2).

Table 4 displays individual tremor scores at baseline and at the 5-year or last follow-up visit in all 19 patients with PD. Analysis of these data indicated that 17 of 19 patients with PD had reduced tremor with stimulation at the 5-year or last follow-up visit compared with baseline. Only two patients experienced a mild increase in tremor (one point) at 5 years postsurgery compared with baseline. At the 5-year or last follow-up visit, all 19 patients exhibited improvement in tremor scores in the stimulation-on condition compared with the stimulation-off condition.

Stimulation Parameters

The stimulation parameters were not significantly changed at the 5-year follow-up visit compared with those at the 1-year visit. At the 5-year follow up in parkinsonian patients receiving unilateral stimulation, the mean ampli-

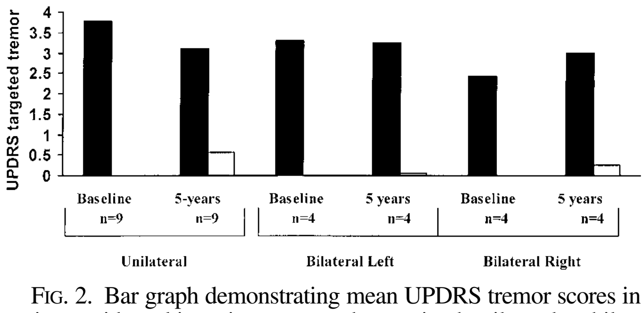

FIG. 2. Bar graph demonstrating mean UPDRS tremor scores in patients with parkinsonian tremor who received unilateral or bilateral thalamic stimulation. Results reflect targeted tremor treated in the targeted limb. Five-year and baseline results are presented only for patients who had complete data at both time points. *Black bars* represent stimulation-off scores; *white bars* represent stimulation-on scores. N = number of patients.

TABLE 3

*Baseline and follow-up UPDRS motor scores in patients receiving unilateral or bilateral thalamic stimulation for parkinsonian tremor**

Variable	Baseline	5-Yr FU		p Value (compared w/ baseline)		p Value (stim off compared w/ stim on)
		Stim Off	Stim On	Stim Off	Stim On	
unilat stim						
no. of patients	10	10	10			
UPDRS						
motor†	38.5 ± 10.7	44.1 ± 10.5	34.3 ± 7.5	0.30	0.28	<0.01
tremor‡	11.9 ± 3.4	13.6 ± 3.9	5.2 ± 3.8	0.41	<0.01	<0.01
rigidity§	3.7 ± 1.3	4.3 ± 2.4	3.8 ± 1.9	0.69	1.00	0.31
bradykinesia‖	14.3 ± 5.4	12.2 ± 6.1	11.8 ± 4.5	0.20	0.11	0.98
bilat stim						
no. of patients	5	5	5			
UPDRS						
motor†	30.4 ± 14.9	44.8 ± 14.6	24.6 ± 4.9	0.31	0.81	0.06
tremor‡	11.2 ± 5.3	16.6 ± 3.0	1.4 ± 0.9	0.19	0.06	0.06
rigidity§	4.2 ± 2.3	4.8 ± 1.6	3.4 ± 0.5	0.81	0.75	0.25
bradykinesia‖	8.0 ± 6.5	11.6 ± 5.7	8.4 ± 3.3	0.63	1.00	0.38
combined						
no. of patients	15	15	15			
UPDRS						
motor†	35.8 ± 12.4	44.3 ± 11.5	31.1 ± 8.1	0.08	0.23	<0.01
tremor‡	11.7 ± 3.9	14.6 ± 3.9	3.9 ± 3.6	0.09	<0.01	<0.01
rigidity§	3.9 ± 1.6	4.5 ± 2.1	3.7 ± 1.6	0.46	0.81	0.05
bradykinesia‖	12.2 ± 6.3	12.0 ± 5.7	10.7 ± 4.4	0.65	0.31	0.53

* Results are based on Wilcoxon signed-rank comparisons of 5-year and baseline scores only in patients who had complete data for both time points.
† Items 18 to 31. Because left- and right-side rigidity scores were combined for both the upper and lower extremities, the total possible motor score was 100 rather than 108.
‡ Items 20 and 21.
§ Item 22. Because left- and right-side rigidity scores were combined for both the upper and lower extremities, the total possible rigidity score was 12 rather than 20.
‖ Items 23 to 26.

tude was 2.6 V, pulse width was 133 μsec, and rate was 154 Hz; 33% of these patients received monopolar stimulation. In parkinsonian patients receiving bilateral stimulation, electrical impulses in the first side had a mean amplitude of 4.4 V, pulse width of 138 μsec, and rate of 166 Hz; 20% of the patients received monopolar stimulation. Electrical impulses in the second side had a mean amplitude of 3.1 V, pulse width of 138 μsec, and rate of 143 Hz; 40% of patients received monopolar stimulation. Stimulation amplitudes at the 3-month and 5-year or last follow-up evaluation in each of the 19 patients with PD are shown in Table 4. The amplitude was increased by at least 1 V in three patients, remained relatively unchanged (< 1 V) in 13, and decreased by at least 1 V in two. In one patient, 3-month stimulation parameters were not available.

Entire Cohort

Some or all data in eight of the 45 patients were missing at the 5-year follow up. Explanations for the missing data in seven patients were listed previously; data regarding the stimulation-on condition only were missing in one additional patient. To determine the potential for bias due to these missing data, the analyses in Table 1 were repeated after substituting data from the latest follow-up visit for the four patients with ET who were missing 5-year data. Although the differences between the average motor tremor score during stimulation-off and -on periods were slightly smaller than in Table 1, in no case was the difference smaller by more than 0.5 point. All comparisons that were statistically significant in Table 1 had the same or lower probability values after substitutions for missing data (results not shown). A similar analysis with substitution of the latest follow-up values for the four patients with parkinsonian tremor who were missing 5-year data was completed for the UPDRS tremor score in Table 3. Differences between the average UPDRS tremor scores during stimulation off and the scores during stimulation on remained virtually unchanged, except that the bilateral difference was less by 0.8 point. The probability values for all three of these comparisons remained less than 0.01. We concluded that the results presented in this report are not biased as a result of the missing data.

Stimulation-Related Adverse Events

Adverse events related to stimulation were reported in more than 10% of patients with unilateral and bilateral thalamic stimulators for ET and PD (Table 5). Most of the adverse events were mild and were reduced with changes in stimulation parameters. In patients with bilateral stimulation, adverse events such as dysarthria and other speech difficulties, disequilibrium or balance difficulties, and abnormal gait persisted despite optimization of the stimulation parameters.

Device-Related Surgical Revisions

Twenty-five patients underwent 50 device component replacement or explantation procedures. Twelve patients (27%) required surgical revisions other than IPG replacements, often involving more than one device component.

TABLE 4

*Changes in tremor score and IPG amplitude in 19 patients with parkinsonian tremor**

		Tremor Score				IPG Amplitude‡	
Case No.	Stim Type	Baseline	5-Yr Stim Off	5-Yr Stim On	% Decrease†	3 Mos Postop	5-Yr FU
1	bilat	15	19	2	89	3.1	3.5
2	bilat	16	13	2	85	2.8	4.0
3	unilat	10	14	1	93	2.3	2.3
4	unilat	15	21	10	52	4.1	4.8
5	bilat	6	20	1	95	5.4	4.8
6§	unilat	7	8	1	88	3.2	3.6
7	unilat	13	9	4	56	NA	2.2
8	bilat	5	14	2	86	3.7	3.8
9§	bilat	16	10	1	90	2.2	2.3
10‖	bilat	19	17	2	88	2.0	3.2
11	bilat	14	17	0	100	4.7	5.8
12‖	bilat	18	25	10	60	4.1	3.3
13	unilat	15	11	5	55	3.2	3.7
14	unilat	9	12	10	17	1.8	2.2§
15	unilat	6	12	4	67	3.5	2.5
16	unilat	15	14	6	57	1.8	2.4
17	unilat	9	19	10	47	5.3	2.2
18	unilat	11	15	0	100	1.5	2.0
19	unilat	16	9	2	78	2.2	1.5

* NA = not available.
† Stimulation-off scores minus stimulation-on scores.
‡ In patients receiving bilateral stimulation, amplitude refers only to the first implanted side.
§ Patient did not have 5-year data; therefore, 4-year data were used.
‖ Patient did not have 5-year data; therefore, 3-year data were used.

Revisions consisted of 10 lead replacements in eight patients, four extension replacements in three patients, one extension explant in one patient, and two IPG explants in two patients. In addition to device explantation or replacement, four patients underwent lead repositioning a total of five times. A loss of effect (worsening of tremor) and the development of side effects such as dysarthria, dystonia, paresthesia, and other sensory disturbances were reported as the most common reasons for these surgical revisions. Twenty patients received 33 IPG replacements. Fourteen of the 33 IPGs were returned to the device manufacturer for evaluation; 12 were at or near the normal end of the battery life and two were functioning per specifications. The 12 confirmed battery depletions occurred at a mean of 2.5 years after implantation. The remaining 19 IPGs were not returned to the device manufacturer for evaluation, but the most commonly reported adverse events leading to their replacement included loss of effect (worsening of tremor), end of battery life, and intermittent stimulation.

Discussion

Data in this study demonstrate long-term tremor control with thalamic stimulation in patients with ET and PD. Study results were analyzed separately based on the diagnosis of ET or PD as well as on whether patients received unilateral or bilateral thalamic stimulation. This methodology resulted in small sample sizes per group and low statistical power for comparisons.

There have been few studies with long-term follow-up data on thalamic stimulation in patients with ET. Sydow, et al.,[11] reported results from a mean follow up of 6.5 years in 19 patients with ET. Twelve of these patients received unilateral thalamic stimulation and seven received bilateral stimulation. The baseline tremor motor scores (TRS Items 1–9) worsened from a baseline score of 17.6 to 19.4 (stimulation off). Similarly, in our study, the baseline tremor motor scores (TRS Items 1–10) in patients receiving unilateral stimulation worsened from 21.5 to 21.7 (stimulation off) at the last follow-up evaluation. Sydow and coworkers reported a 46% improvement in the stimulation-on condition compared with stimulation-off scores at the long-term follow up—compared with the improvement of 46% reported in our study. However, Sydow and colleagues combined patients who received unilateral and bilateral thalamic stimu-

TABLE 5

*Most common adverse events in patients with ET and PD**

	ET		PD	
Variable	Unilat	Bilat	Unilat	Bilat
no. of patients	18	8	11	8
pain	33	25	55	38
paresthesia	56	25	27	13
dysarthria	17	63	9	88
incoordination	17	38	27	75
dysphagia	6	13	27	75
asthenia	22	25	9	13
depression	11	0	27	38
hypertonia	6	0	45	13
increased salivation	6	0	18	50
abnormal thinking	17	13	18	13
insomnia	6	25	27	0
speech disorder	11	25	9	13
accidental injury	17	13	9	0
abnormal gait	0	25	18	13
bone fracture	6	25	9	13
bradykinesia	0	0	27	25
hallucinations	11	0	9	25
headache	17	0	9	13
hypophonia	6	25	9	13
somnolence	6	25	0	25

* Numbers represent the percentage of patients having a particular adverse event.

lation. The patients who received bilateral thalamic stimulation in our study had a 78% improvement in the mean tremor motor scores on follow up compared with those at baseline. Sydow and associates reported a 39% improvement in ADL scores compared with baseline. The patients in our study who received unilateral thalamic stimulation had an improvement of 51% and those who received bilateral stimulation had an improvement of 36% in the mean follow-up ADL scores compared with baseline scores.

There are also few studies with long-term evaluation of thalamic stimulation for PD. Rehncrona, et al.,[10] reported results in 12 patients with PD who completed a mean follow-up period of 6.6 years. The UPDRS motor scores at baseline were 28 as opposed to the follow-up scores of 43 in the stimulation-off state and 34 in the stimulation-on condition. In our series, combining results of unilateral and bilateral procedures, the mean UPDRS motor scores worsened from 35.8 at baseline to 44.3 in the stimulation-off state over a period of 5 years. The mean UPDRS motor score in the stimulation-on state was 31 at 5 years postsurgery. Like us, Rehncrona and colleagues reported worsening bradykinesia and rigidity scores as well as a significant improvement in tremor scores at the long-term follow-up visit.

Our long-term stimulation parameters did not change significantly over 5 years, an occurrence similarly reported in other long-term studies.[10,11] Sydow and colleagues[11] have reported a mean amplitude of 2.6 V, a pulse width of 88.8 μsec, and a rate of 173 Hz in patients with ET; Rehncrona and associates[10] reported a mean amplitude of 2.2 V, a pulse width of 90.4 μsec, and a rate of 160 Hz.

Adverse effects related to unilateral stimulation in patients with ET included paresthesias, dysarthria, disequilibrium or balance difficulties, cognitive problems, and asthenia. Many of these adverse effects were improved by adjusting the stimulation parameters. In patients receiving bilateral stimulation for ET, however, dysarthria, disequilibrium or balance difficulties, other speech disorders, and abnormal gait were more common than in patients who received unilateral stimulation. A greater percentage of bilaterally stimulated patients reported bone fractures compared with unilaterally stimulated patients, possibly indicating a greater incidence of falls. Therefore patients with ET should be cautioned against bilateral implantation due to the high potential for speech and gait difficulties.

In patients with PD receiving unilateral thalamic stimulation, disequilibrium or balance difficulties, dysphagia, cognitive difficulties, and abnormal gait were the most common adverse effects, which could be managed by an adjustment of the stimulation settings. In patients receiving bilateral thalamic stimulation, dysarthria, disequilibrium or balance difficulties, dysphagia, and increased salivation were the most commonly reported adverse events, and these events occurred more often in bilaterally stimulated patients compared with unilaterally stimulated patients.

Twelve (27%) of the 45 patients in this study required surgical revisions other than IPG replacements. The hardware-related events in this study are similar to those reported in other long-term series.[10,11]

Conclusions

Unilateral thalamic stimulation can be recommended for long-term management of ET, whereas bilateral thalamic stimulation should be used cautiously due to potential axial adverse effects related to stimulation, such as dysarthria and gait and postural problems. Thalamic stimulation should not be recommended routinely for parkinsonian tremor, given the lack of benefit in bradykinesia and rigidity and the likelihood of further progression of these symptoms, unless the PD is tremor-predominant with little functional disability due to other symptoms. Furthermore, bilateral thalamic stimulation causes significant adverse effects that limit therapeutic efficacy.

Disclosure

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