Randomized Trial of Pallidotomy versus Medical Therapy for Parkinson's Disease

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Thirty-six patients with Parkinson's disease (PD) were randomized to either medical therapy (N = 18) or unilateral GPi pallidotomy (N = 18). The primary outcome variable was the change in total Unified Parkinson's Disease Rating Scale (UPDRS) score at 6 months. Secondary outcome variables included subscores and individual parkinsonian symptoms as determined from the UPDRS. At the six month follow-up, patients receiving pallidotomy had a statistically significant reduction (32% decrease) in the total UPDRS score compared to those randomized to medical therapy (5% increase). Following surgery, patients' showed improvement in all the cardinal motor signs of PD including tremor, rigidity, bradykinesia, gait and balance. Drug-induced dyskinesias were also markedly improved. Although the greatest improvement occurred on the side contralateral to the lesion, significant ipsilateral improvement was also observed for bradykinesia, rigidity and drug-induced dyskinesias. A total of twenty patients have been followed for 2 years to assess the effect of time on clinical outcome. These patients have shown sustained improvement in the total UPDRS ($p < 0.0001$), "off" motor ($p < 0.0001$) and complications of therapy subscores ($p < 0.0001$). Sustained improvement was also seen for tremor, rigidity, bradykinesia, percent on time and drug-induced dyskinesias.

Ann Neurol 2003;53:558–569

Over the past decade, there has been a marked resurgence of interest in surgery for Parkinson's disease (PD). Several factors have contributed to this: (1) the need for better therapies to treat the continued worsening of parkinsonian motor symptomatology and the development of drug-induced dyskinesias and motor fluctuations, (2) advances in our understanding of the physiological basis of parkinsonism and the rationale for surgery,[1,2,4] and (3) the report by Laitinen and colleagues of improvement in parkinsonian motor signs after pallidotomy.[3]

Although there are now numerous reports on the benefits of pallidotomy for PD,[5–15] there has been only one randomized clinical trial comparing the effects of pallidotomy to best medical therapy.[16] In some of the previous studies, nontremulous[7] or predominately asymmetric[6] patients were selected, whereas in others nonstandardized methods of clinical evaluation were used.[10,12,13] Therefore, it is difficult to compare the results of pallidotomy across studies and to assess the effect of pallidotomy for patients regardless of symptom profile.

We present here the results of a randomized, prospective clinical trial comparing the effectiveness of pallidotomy to best medical management in patients followed up for 6 months. In addition, we present data for the first 20 patients who have been followed up for 2 years.

Patients and Methods

Patient Recruitment and Assessment

Patients were recruited from the Movement Disorders Center at Emory and Grady Memorial Hospital Clinics. To limit patient attrition, we limited the geographical location for patient recruitment to a 500-mile radius from the City of Atlanta.

Patients were screened with a detailed history and physical examination by a movement disorders neurologist. Inclusion criteria consisted of (1) a clinical diagnosis of idiopathic PD (based on the presence of at least two of the three [bradykinesia, tremor, and rigidity] cardinal signs of PD), with a history and clinically documented good response to L-dopa therapy; (2) Hoehn and Yahr stage III or greater when "off"; (3) motor fluctuations (severe "on–off" periods) or dyskine-

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Received Apr 23, 2001, and in revised form Dec 3, 2002. Accepted for publication Dec 7, 2002.

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sias; and (4) an unsatisfactory clinical response to maximal medical management.

Patients were excluded if there was (1) evidence of secondary or atypical parkinsonism as suggested by (a) a history of cerebrovascular accidents, encephalitis, exposure to toxins, or neuroleptics, (b) supranuclear gaze palsy or neurological signs of upper motor neuron or cerebellar involvement, (c) magnetic resonance imaging (MRI) scan with evidence of significant cortical, cerebellar, or brainstem atrophy, lacunar infarcts, or iron deposits in the putamen, (d) poor response to L-dopa by history and examination; (2) clinically significant medical disease (eg, cardiac disease, uncontrolled hypertension, coagulopathies) that would increase the risk of developing preoperative or postoperative complications; or (3) evidence of significant dementia using the Mattis Dementia Rating Scale score of <116 (three standard deviations below the mean) or refractory depression. Patients with scores on the Hamilton Depression Rating Scale greater than 14 or meeting Diagnostic and Statistical Manual of Mental Disorders (DSM)–IIIR criteria for major depression were referred for treatment of depression. These patients were allowed to enter the study after a 1-month remission from depressive symptoms.

Informed consent was obtained from all patients who agreed to participate in the study. All patients had their medication optimized for at least 1 month before their first baseline evaluation. After the baseline evaluations, medication adjustments were made only if considered necessary to maintain the optimal clinical response. L-Dopa equivalence was calculated based on the formula of carbidopa-leuodopa 25/100 = 100mg L-dopa; controlled release carbidopa-leuodopa 25/100 = 65mg L-dopa; controlled release carbidopa-leuodopa 50/200 = 130mg L-dopa; pramipexole 1mg = 100mg L-dopa; ropinirole 1mg = 20mg L-dopa; pergolide 1mg = 100mg L-dopa and bromocriprine 10mg = 100mg L-dopa.[17,18]

Formal visual field testing was conducted before and after surgery. Patients underwent formal neurological, psychiatric, detailed neuropsychological evaluations, and quantitative tests of motor performance at baseline, 3, 6, and 12 months, and yearly thereafter. Two independent neurologists, with extensive experience, evaluated patients using the Core Assessment Program for Intracerebral Transplantation (CAPIT) protocol, which includes the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr staging, and timed tests of motor function. Except for visual field testing, which was performed in the outpatient clinic, all assessments were performed in the clinical research center (CRC) over 3 days. The first day in the CRC allowed patients to adapt to the CRC environment and optimize the chances of recording their "best on" response the following morning. On day 2, the patients "best on," (ie, after the patients' morning medication) was assessed. The patient's morning medication was supplemented when necessary to obtain a "best on," if a full response was not obtained initially. The morning of day 3 the patients "worst off" (ie, "off" all antiparkinsonian medications for at least 12 hours) was assessed.

The evaluating neurologists had no contact with the patients between visits, had no involvement in their ongoing care, and were blinded as to the treatment modality by having the patients wear hats during their stay in the CRC. Patients also were instructed not to inform the examining neurologists which group they were in. Three baseline evaluations were performed on all patients at monthly intervals. The mean of the baseline data was used for all calculations involving comparisons to follow-up data. At the conclusion of the second baseline evaluation, patients were randomized to either medical management or surgery.

Patients randomized to surgery underwent pallidotomy within 1 month of their third baseline evaluation. Patients randomized to best medical therapy were reevaluated at 3 and 6 months after their third baseline visit and were given the option to receive pallidotomy after their 6-month evaluation. Those who then chose surgery (all patients did so) also were evaluated at 3, 6, and 12 months after pallidotomy and at yearly intervals thereafter.

The primary outcome variable was the average change in the total UPDRS score at 6 months. The total UPDRS was calculated as the sum of subscores I–IV with subscores II and III in the off state. Secondary outcome variables included: subscores from the UPDRS, timed tests of motor behavior, dyskinesias, Hoehn and Yahr staging, Modified Schwab and England Activities of Daily Living Scale, and neuropsychological and psychiatric evaluations. Motor fluctuations were calculated by summing questions 36 to 39 (subsection IV of the UPDRS). Based on the side of the lesion, contralateral and ipsilateral scores for tremor, rigidity, and dyskinesia were determined by summing the scores for arm and leg. The baseline contralateral and ipsilateral data for medical control was determined based on which side was lesioned after completion of medical management.

To further evaluate the effect of pallidotomy on tremor, we examined the effect of pallidotomy on a subset of patients with moderate to severe tremor (summed arm plus leg tremor scores ≥2). Patients from the medical management group who had completed their 6-month follow-up postpallidotomy (crossover patients) were included with patients from the surgical group to provide a higher number of patients for this analysis. The effect of pallidotomy on lower and upper extremity bradykinesia was assessed using question 26 of the UPDRS and timed tests of motor behavior. The assessment of body bradykinesia and hypokinesia was determined by question 31 of the UPDRS. Gait and postural stability were assessed using questions 29 and 30 of the UPDRS together with timed tests of walking, that is, stand-walk-sit test.

The neuropsychological evaluations included: Mattis Dementia Rating Scale, California Verbal Learning Test, Warrington Recognition Memory Test, Wechsler Memory Scale–Revised, Wisconsin Card Sorting Test, Letter Fluency, Category Fluency, Stroop Test, Finger Tapping, Purdue Pegboard, Boston Naming Test, and Judgement of Line Orientation. The psychiatric evaluation consisted of a structured clinical interview for DSM-IIIR, the Geriatric Depression Scale, "inclusive" (patient's affective status including the impact of PD on affective symptoms), and "etiologic" (affective symptoms apart from the impact of the disease) Hamilton Depression and Anxiety Rating Scales, the Spielberger State Anxiety Inventory, the Spielberger Trait Anxiety Inventory, and a patient self-related sexual functioning questionnaire.

Surgical Technique

All drugs potentially affecting coagulation times were stopped for at least 2 weeks before surgery. Bleeding times were assessed in all patients as part of the preoperative evaluation. All antiparkinsonian medications were withheld after midnight, on the day of surgery, to prevent the development of drug-induced dyskinesias during placement of the stereotaxic frame and allow parkinsonian motor signs to emerge for intraoperative assessment of the effect of the lesion.

Placement of the head frame and MRI imaging for the selection of initial target coordinates have been described in a previous publication as have the details of targeting, the equipment, microelectrode mapping, and the lesioning technique.[19]

Lesion location was determined postoperatively from high-resolution thin-slice MRI imaging reconstructions. The location of the lesion relative to the anterior and posterior borders of GPi and adjacent structures was determined from the high-resolution three-dimensional reconstructions. Lesion volumes also were calculated from these reconstructions using the three-dimensional volumetric analysis program Brainworks.

Statistical Analysis

BASELINE COMPARISON. Demographic and clinical characteristics of the surgery and medical management groups were compared at baseline. The χ^2 test or Fisher's exact test was used to determine the significance of differences in categorical variables, and the Student's *t* test or Wilcoxon two sample test was used for continuous variables.[20]

THREE- AND 6-MONTH OUTCOMES. Each secondary outcome variable was measured at baseline and after 3 and 6 months. For each outcome variable, we conducted a repeated measurements analysis with each of the two follow-up measurements at 3 and 6 months. The independent variables were the surgical or medical management group, the baseline value of the corresponding outcome, time (3 or 6 months), age and the group by time interaction. The group by time interaction was tested first. If there was a significant interaction effect, we conducted separate comparisons between the two groups at each time point. Otherwise, we conducted only a single comparison between the groups. The analysis was performed by the generalized estimation equations approach,[21] which provides robust results while accounting for the correlation among the repeated measurements within each patient. We used PROC GENMOD from the SAS software release 6.12. All tests were two tailed, and each reported *p* value corresponds to a single comparison. A *p* value less than 0.05 was considered significant.

TWO-YEAR OUTCOME. For patients randomized to the surgical group, we used each patient's outcome measurements at baseline, 3, 6, 12, and 24 months. For patients in the medical management group who crossed over to surgery, we used their 6-month medical management follow-up as the baseline data for surgical follow-up. Two analyses were conducted. In the first analysis, we compared the 2-year outcome with the baseline data by paired *t* test. In the second analysis, we investigated the change in the outcome variable over time, where time is a continuous variable taking values of 3, 6, 12, and 24. As before, we used the generalized estimation equation method to account for the correlation of the repeated measurements conducted on the same patient.

Results

Baseline Characteristics

Thirty-six patients who met entry criteria were randomized in the study. The data and safety monitoring committee, after review of the third interim analysis, recommended to stop randomization based on the strong evidence supporting the effectiveness of pallidotomy over medical management. The demographic data and patient characteristics across the two study groups were similar except for the motor examination "off" score, which was slightly higher in the surgery group (Table 1). Two patients dropped out of the study. One surgical patient was unable to continue follow-up after the 3-month postoperative evaluation because of transportation problems, and one medical control was unable to take time off from work to complete the CRC evaluations. In addition, one medical control was excluded from the primary outcome analysis. Surgery was performed before the 6-month medical follow-up because of problems with insurance coverage; however, the patient continued to participate in postsurgical follow-up.

Primary Outcome Variable

UNIFIED PARKINSON'S DISEASE RATING SCALE. The reliability coefficient for the three baseline measurement was 0.78, and the standard error of the mean over patients based on the averages of three baseline evaluations per patients compared with a single baseline evaluation per patient were 3.4 and 3.6, respectively. Thus, there was little variability in the three baseline evaluations in this patient population. Compared with medical management, patients in the surgical group had significantly reduced total UPDRS scores at the 6-month follow-up ($p < 0.0001$). The surgical group had an average improvement of 32% (Fig. 1a), whereas the medical management group worsened an average of 5% (Fig. 1b) over the 6-month follow-up.

Secondary Outcome Variables

For the surgical group, motor "off" scores, section III of the UPDRS, improved 32%, whereas scores for the medical management group showed a small increase at the 6-month evaluation. In the surgery group, tremor was present in the "off" state on the contralateral side in 10 of 17 patients preoperatively. In seven of these patients, tremor was completely abolished at 6 months postoperatively, whereas in three patients tremor was essentially unchanged (Fig 2a). The medical control group did not experience a significant change in tremor scores.

Table 1. Baseline Characteristics[a]

Characteristics	Surgery (N = 18) (%)	Medical Management (N = 18) (%)	*p*
Demographic			
Age (yr), mean ± SD	56.7 ± 9.0	59.9 ± 8.3	0.27
Gender			0.48
Female	5 (27.8)	7 (38.9)	
Male	13 (72.2)	11 (61.1)	
Race			1.00
Black	1 (5.6)	1 (5.6)	
White	17 (94.4)	17 (94.4)	
Years since PD diagnosis (mean ± SD)	12.3 ± 4.0[b]	13.5 ± 4.1	0.40
Lesion			0.51
Left	11 (61.1)	8 (50.0)	
Right	7 (38.9)	8 (50.0)	
Clinical (mean ± SD)			
UPDRS–total	80.8 ± 17.7	70.9 ± 16.9	0.093
UPDRS–motor “off”	43.3 ± 10.7	35.7 ± 11.0	0.043
UPDRS–motor “on”	18.2 ± 9.2	15.5 ± 7.7	0.34
UPDRS–ADL “off”	25.1 ± 6.8	23.6 ± 6.3	0.50
UPDRS–ADL “on”	11.6 ± 4.9	11.8 ± 6.1	0.94
UPDRS–mentation and mood	2.3 ± 1.2	2.3 ± 1.3	0.92
UPDRS–complications of therapy, past week	10.0 ± 2.8	9.6 ± 3.2	0.66
Hoehn and Yahr “off”	4.2 ± 0.4	4.1 ± 0.4	0.45
Schwab and England–ADL “off”	48.4 ± 17.0	52.6 ± 14.8	0.43

[a]Tabulation by treatment group.
[b]n = 17.

SD = standard deviation; PD = Parkinson’s disease; UPDRS = Unified Parkinson’s Disease Rating Scale; ADL = Activities of Daily Living.

In the 10 patients with moderate to severe tremor (summed arm plus leg tremor score ≥2, see Patients and Methods), the total tremor score decreased on the contralateral side from 2.8 to 0.4 after pallidotomy, with 7 patients showing complete resolution of tremor at 6 months postoperatively (see Fig 2b).

Contralateral rigidity in the surgical group was decreased in 15 of the 17 patients. Contralateral “off” rigidity scores improved an average of 55%, whereas ipsilateral scores improved 41% at the 6-month postoperative follow-up (Table 2). For seven patients in the surgery group with moderate rigidity (summed arm and leg rigidity score ≥4.0), rigidity scores decreased an average of 70% postpallidotomy (Fig 3). The medical control group showed no significant change in rigidity (see Table 2).

After pallidotomy, upper extremity bradykinesia and movement times (two-point movement) were significantly decreased on the contralateral side, both in the “off” and “on” states with an average improvement of 39 and 27%, respectively (see Table 2). Significant improvement in two-point movement also was observed in the ipsilateral arm in the “off” condition, improving an average of 28%. Although timed tests for alternating fingers and pronation-supination also improved after pallidotomy, this was not significant compared with the medical control group and may reflect the larger standard deviation associated with these tests.

Improvements in “off” bradykinesia scores for the surgical group also were observed in the lower extremities. Foot tapping was improved 36% (2.5 ± 1.0 → 1.6 ± 1.1) on the contralateral side and 29% (2.4 ± 1.0 →1.0 > ± 1.3) on the ipsilateral side. In contrast, contralateral foot tapping scores at the 6-month follow-up were unchanged (2.3 ± 1.1 → 2.2 ± 1.2) in the medical control group.

Gait and postural stability were significantly improved at 6 months in both “off” and “on” states in the surgical group, whereas the medical group tended to remain the same or worsen (see Table 2). Compared with baseline, “off” gait and postural stability scores in the surgical group improved an average of 32 and 34%, respectively.

In the timed stand-walk-sit test, before surgery, six patients in the surgical group were unable to perform the test when “off,” whereas two required greater than 60 seconds to complete the test. After pallidotomy, five of these eight patients were able to complete the test with an average time of 19.6 seconds. Of the nine patients in the surgical group who were able to perform the test at baseline, the average score decreased from 23.7 to 12.9 seconds. In the medical management group, three patients were unable to perform the stand-walk-sit test at baseline, and by the 6-month follow-up seven patients were unable to perform this test. Interestingly, eight patients in the medical control group

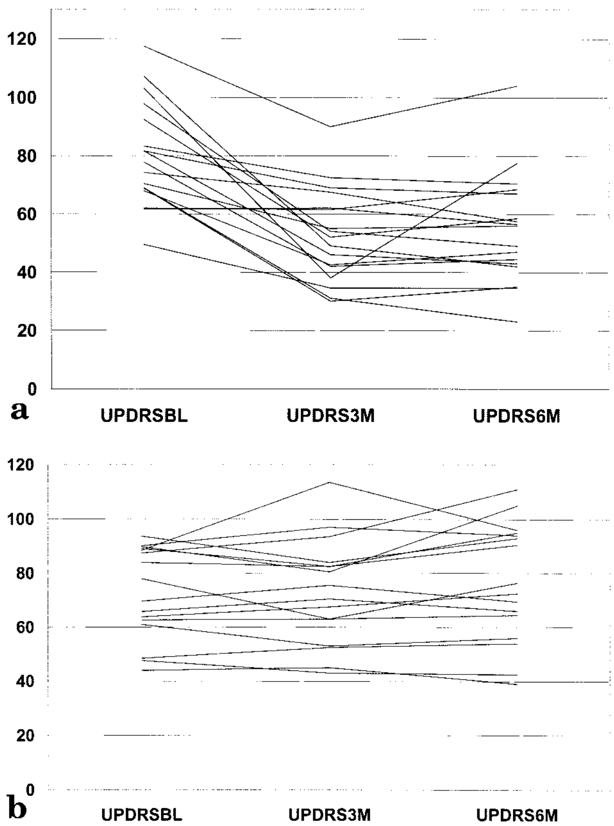

Fig 1. Representation of individual Unified Parkinson's Disease Rating Scale (UPDRS) scores for patients in the (a) surgical and (b) medical management groups from baseline to 6-month follow-up.

showed an average improvement of 21.6 to 15.4 seconds at the 6-month follow-up. Freezing was also significantly improved in the surgical group ($p < 0.0032$).

In the surgical group, the UPDRS–Activities of Daily Living "off" was significantly improved, an average of 23%, whereas the medical control group worsened an average of 5% (see Table 2). The Activities of Daily Living "on" score did not show significant group differences. Patients undergoing pallidotomy also demonstrated a significant improvement in both the Hoehn and Yahr and the Schwab and England score of functional independence when compared with medical management ($p < 0.0001$; see Table 2).

Patients in the surgical group experienced an average weight gain of 5kg. Patients in the medical control group lost an average of 0.8kg. There was no correlation between the amount of weight gain and improvement in dyskinesias.

MEDICATION. There was no significant change in L-dopa equivalence from baseline to the 6-month follow-up. Patients in the surgical group took an average of 1,147mg of L-dopa equivalence at baseline and remained at an average of 1,142mg at 6 months, whereas the medical control group took an average of 882mg at baseline and 945mg of L-dopa at their 6-month follow-up. Compared with medical management, there was a significant reduction in both the "percentage of off time" as well as the complication of therapy subscore from the UPDRS (see Table 2).

DRUG-INDUCED DYSKINESIAS AND MOTOR FLUCTUATIONS. Motor fluctuations and the dyskinesia scale score were significantly lower in the surgery group (see Table 2). Of 17 patients with dyskinesias in the surgical group, all 17 improved postoperatively and 12 had complete relief. Ipsilateral dyskinesias were reduced an average of 36%. In the medical management group, dyskinesias were worse in 10 of the patients at the 6-month follow-up, with an overall worsening of 8%.

Neuropsychological Assessments

At the 6-month assessment, the surgery group did not differ from the medical management group on most

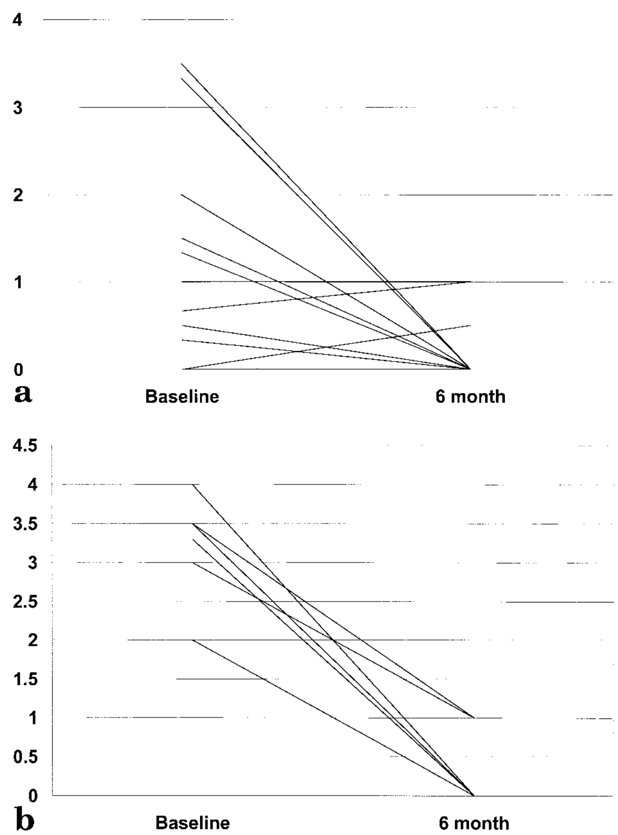

Fig 2. Individual "off" tremor (arm plus leg) score from the Unified Parkinson's Disease Rating Scale for patients in the surgical and medical management groups for the (a) contralateral side and (b) contralateral side for crossover data. Crossover data are derived from patients randomized to surgery and those in the medical control group after pallidotomy whose summed tremor scores were 2 or higher and had been followed up for at least 6 months after pallidotomy.

Table 2. Baseline versus 6 Month Follow-up (mean ± SD)

Clinical Characteristics	Surgical		Medical Management		p
	Baseline	6-Month Follow-up	Baseline	6-Month Follow-up	
UPDRS					
Total	80.4 ± 18.2	54.9 ± 19.1	72.8 ± 17.0	76.6 ± 22.1	<0.0001
Motor "off"	43.2 ± 11.0	28.7 ± 9.8	36.9 ± 10.8	38.4 ± 14.6	0.0002
Motor "on"	18.4 ± 9.5	16.6 ± 7.6	16.2 ± 7.9	16.4 ± 8.7	0.32
ADL "off"	24.7 ± 6.7	18.9 ± 9.3	24.3 ± 6.1	25.6 ± 7.7	<0.0001
ADL "on"	11.5 ± 5.0	10.3 ± 7.4	12.0 ± 5.8	14.3 ± 6.0	0.11
Mentation and mood	2.2 ± 1.2	1.7 ± 1.5	2.4 ± 1.3	2.3 ± 1.6	0.053
Complications of therapy	10.2 ± 2.8	5.6 ± 2.3	9.5 ± 3.3	10.2 ± 2.7	<0.0001
Motor fluctuation	4.38 ± 1.06	3.00 ± 1.19	4.23 ± 1.01	4.25 ± 1.00	<0.0001
Tremor–contralateral					
"Off"	0.9 ± 1.1	0.2 ± 0.4	1.7 ± 1.7	1.6 ± 1.5	0.0007
"On"	0.2 ± 0.5	0.0 ± 0.0	0.6 ± 1.3	0.4 ± 0.9	NS
Tremor–ipsilateral					
"Off"	0.8 ± 1.5	0.5 ± 0.9	1.0 ± 1.4	0.9 ± 1.2	NS
"On"	0.1 ± 0.3	0.1 ± 0.5	0.2 ± 0.5	0.1 ± 0.4	NS
Rigidity–contralateral					
"Off"	3.6 ± 1.5	1.6 ± 1.2	2.4 ± 1.3	2.3 ± 1.7	0.0003
"On"	1.1 ± 1.1	0.7 ± 0.7	0.8 ± 1.1	0.4 ± 0.8	NS
Rigidity–ipsilateral					
"Off"	3.2 ± 1.3	1.9 ± 1.5	2.2 ± 1.2	2.1 ± 1.7	0.057
"On"	1.2 ± 1.1	1.0 ± 0.9	0.7 ± 0.9	0.4 ± 0.8	NS
Bradykinesia body					
"Off"	3.2 ± 0.5	2.4 ± 0.9	3.0 ± 0.7	3.0 ± 0.8	0.0041
"On"	1.2 ± 0.8	1.2 ± 0.8	1.3 ± 1.0	1.1 ± 1.0	0.06
Pronation supination–contralateral					
"Off"	23.9 ± 10.0	17.9 ± 3.6	18.2 ± 3.2	17.9 ± 4.4	NS
"On"	17.9 ± 5.4	17.5 ± 4.3	17.7 ± 7.5	16.5 ± 7.0	NS
Pronation supination–ipsilateral					
"Off"	20.6 ± 5.8	18.6 ± 5.0	18.1 ± 3.7	18.1 ± 4.4	NS
"On"	17.0 ± 4.3	17.7 ± 5.2	16.0 ± 3.1	14.5 ± 1.8	0.0075
Alternating fingers–contralateral					
"Off"	20.4 ± 5.4	16.7 ± 4.3	20.4 ± 7.9	18.1 ± 5.6	NS
"On"	16.9 ± 4.0	17.0 ± 6.4	17.2 ± 6.0	17.6 ± 7.5	NS
Alternating fingers–ipsilateral					
"Off"	17.6 ± 3.8	18.5 ± 8.7	17.8 ± 4.8	17.4 ± 4.2	NS
"On"	15.8 ± 3.8	15.9 ± 4.1	15.7 ± 3.9	15.1 ± 3.6	NS
Two points–contralateral					
"Off"	11.0 ± 5.4	6.7 ± 4.3	12.3 ± 7.9	9.6 ± 5.6	0.0015
"On"	9.1 ± 4.0	6.6 ± 6.4	9.4 ± 6.0	9.1 ± 7.5	0.04
Two points–ipsilateral					
"Off"	10.6 ± 3.7	7.6 ± 2.6	10.5 ± 3.4	11.1 ± 5.7	0.0011
"On"	8.5 ± 2.6	6.7 ± 2.0	8.6 ± 2.7	7.1 ± 2.3	NS
Postural stability					
"Off"	1.7 ± 0.7	1.1 ± 0.7	1.7 ± 1.0	2.0 ± 1.3	0.002
"On"	0.9 ± 0.5	0.8 ± 0.7	0.9 ± 0.5	0.9 ± 0.5	0.0056
Gait					
"Off"	2.5 ± 0.9	1.7 ± 1.2	2.2 ± 1.1	2.2 ± 1.2	0.0002
"On"	0.8 ± 0.7	0.6 ± 0.6	0.7 ± 0.7	1.0 ± 0.9	0.0025
Freezing					
"Off"	2.1 ± 1.4	1.7 ± 1.5	2.3 ± 0.9	2.5 ± 1.1	<0.0032
"On"	0.5 ± 0.6	0.7 ± 1.0	1.1 ± 1.1	1.1 ± 1.1	NS
Dyskinesia scale score					
Contralateral	2.4 ± 0.9	0.6 ± 0.9	2.1 ± 1.0	2.2 ± 0.9	<0.0001
Ipsilateral	2.2 ± 0.9	1.4 ± 1.0	1.6 ± 1.0	1.7 ± 1.1	0.0001
Hoehn and Yahr					
"Off"	4.1 ± 0.4	3.2 ± 0.8	4.1 ± 0.4	4.1 ± 0.8	<0.0001
"On"	2.8 ± 0.7	2.5 ± 0.8	2.9 ± 0.4	3.0 ± 0.5	0.047
Schwab and England–ADL					
"Off"	50.3 ± 14.9	71.5 ± 14.2	51.0 ± 14.2	50.9 ± 21.3	<0.0001
"On"	79.3 ± 7.9	86.2 ± 11.3	75.9 ± 7.6	72.5 ± 11.5	0.0001

SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale; ADL = Activities of Daily Living; NS= not significant.

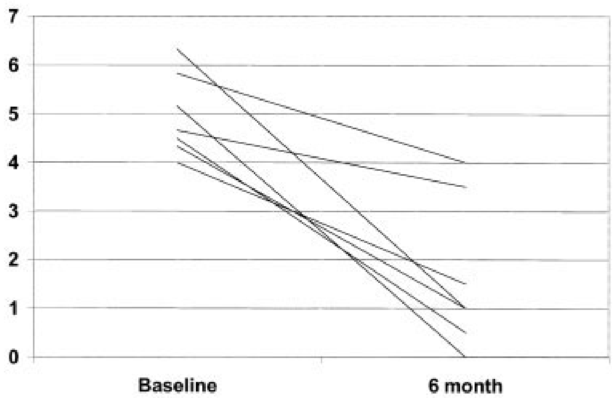

Fig 3. Individual "off" rigidity scores (arm plus leg) from surgical patients with moderate rigidity (summed arm plus leg score ≥4).

measures of neuropsychological function. The surgery group as a whole showed a small, but significant decline on letter fluency ($p < 0.01$) in comparison with the medical management group. However, the surgery group performed better than the medical management group on the Boston Naming Test ($p < 0.01$). The surgery group showed significantly poorer performance on the California Verbal Learning Test long-delay free recall and category fluency than the medical management group at the 3-month follow-up ($p < 0.05$ and $p < 0.01$, respectively), but the two groups did not differ at 6 months. Details of neuropsychological and psychiatric findings, including lesion laterality effects, have been published previously.[22]

Psychiatric Assessments

During the 6 months after randomization, 5 of the 16 medical management patients and 2 of 17 surgical patients met DSM-IIIR criteria for major depression. Of these 7, 6 had a history of major depression.

Psychiatric data were examined to determine whether there was a significant change in the depressive or anxiety symptoms in the population of patients receiving left or right lesions versus the medical control group. When the analyses were controlled for motor improvement with the motor "off" scores, the only significant changes noted were in the self-rated anxiety scores. The right lesion group scored significantly lower (ie, less anxiety) than the medical control on both the SSAI "on" medication ($p = 0.03$) and the STAI ($p = 0.03$). The left lesion group scored significantly lower on the SSAI "on" medication ($p = 0.05$). There were no other differences in the depression or anxiety scores for the three groups.

Complications

Complications occurred in three patients. One patient developed focal motor seizures in the operating room beginning in the contralateral face and involving the contralateral arm and leg, which necessitated discontinuation of the procedure. Subsequently, a pallidotomy was performed; however, the patient again, despite being given phenytoin prophylactically, developed focal motor seizures intraoperatively. This patient was kept on anticonvulsant therapy over the 6-month follow-up period and has been on anticonvulsant therapy over the remaining follow-up period. Another patient developed what was described as a "seizure" that consisted of a staring episode with facial grimacing. She was not treated with anticonvulsants and did well postoperatively. Finally, one patient developed a subcortical hemorrhage in the region of the pallidum during or shortly after lesioning. This patient exhibited a transient worsening in speech as determined by examiner evaluation, which had resolved by the 6-month evaluation. These patients experienced a 22, 31, and 50% reduction in total UPDRS at 6 months. In addition, two patients had small asymptomatic cortical hemorrhages and one had a small asymptomatic subcortical hemorrhage that was detected on the postoperative MRI imaging. There were no visual field deficits detected in any of the patients after pallidotomy.

Lesion Characteristics

Lesion sizes averaged 6 × 5mm in the anterior to posterior and medial to lateral direction, respectively. On average, lesions extended from approximately 7.6 to 13.5mm posterior to the anterior commissure. In the medial to lateral direction, lesions began an average of 18.6mm and extended to an average of 23.6mm from the midline. The average lesion volume was 174mm^3 (range, 95–295mm^3). All lesions included the sensorimotor portion of GPi; however, in two cases there was also significant involvement of adjacent portions of the GPe. In one, this was caused by a hemorrhage at the lesion site that incorporated portions of the striatum as well as the pallidum.

Two-Year Data

Twenty of the patients enrolled in the study (n = 12 surgical, n = 8 medical) have been followed up for 2 years post pallidotomy. The medical control excluded from the primary outcome analysis is included here using the 3-month medical follow-up as baseline. In this patient cohort, we have observed sustained benefit over the 2-year follow-up period in the total UPDRS, "off" motor, and complications of therapy subscores (Table 3). Contralateral tremor, rigidity, and timed tests of the upper extremities, that is, two-point movement, alternating finger tapping, and pronation-supination, as well as drug-induced dyskinesias also remained significantly improved. Gait and postural stability scores, although significantly improved for the group at the 1-year follow-up, were no longer significant at 2 years.

Table 3. Two-Year Follow-up versus Baseline (n = 20 surgical patients) (mean ± SD)

Clinical Characteristic	Baseline	24 Month Follow-up	*p*
UPDRS			
Total	75.5 ± 16.2	59.5 ± 15.4	<0.0001
Motor "off"	39.2 ± 12.9	29.4 ± 9.5	<0.0001
Motor "on"	16.0 ± 9.1	17.2 ± 8.5	NS
ADL "off"	23.9 ± 6.0	21.7 ± 7.1	NS
ADL "on"	12.9 ± 6.0	12.2 ± 6.5	NS
Mentation and mood	2.5 ± 1.5	2.1 ± 1.8	NS
Complications of therapy	9.8 ± 2.4	6.3 ± 2.4	<0.0001
Tremor–contralateral			
"Off"	0.9 ± 1.0	0.2 ± 0.5	0.0016
"On"	0.6 ± 0.4	0.0 ± 0.0	NS
Tremor–ipsilateral			
"Off"	0.4 ± 1.1	0.6 ± 1.4	NS
"On"	0.1 ± 0.3	0.4 ± 1.0	NS
Rigidity–contralateral			
"Off"	3.3 ± 1.5	1.2 ± 1.3	<0.0001
"On"	1.0 ± 1.2	0.4 ± 0.7	0.0006
Rigidity–ipsilateral			
"Off"	3.1 ± 1.5	1.4 ± 1.3	<0.0001
"On"	1.0 ± 1.1	0.4 ± 0.9	0.0014
Bradykinesia body			
"Off"	3.1 ± 0.7	2.3 ± 0.7	<0.0001
"On"	1.1 ± 0.8	1.3 ± 0.8	NS
Pronation/supination–contralateral			
"Off"	21.9 ± 8.7	16.3 ± 4.0	0.012
"On"	18.0 ± 5.7	19.3 ± 4.4	NS
Pronation/supination–ipsilateral			
"Off"	20.3 ± 6.6	20.9 ± 5.6	NS
"On"	17.0 ± 4.1	18.7 ± 3.9	0.032
Alternating fingers–contralateral			
"Off"	20.5 ± 6.3	17.7 ± 5.0	0.0002
"On"	18.9 ± 7.4	18.7 ± 4.9	NS
Alternating fingers–ipsilateral			
"Off"	18.5 ± 4.9	18.5 ± 5.3	NS
"On"	17.6 ± 5.5	18.6 ± 5.5	NS
Two points–contralateral			
"Off"	10.6 ± 4.1	6.8 ± 3.6	<0.0001
"On"	9.9 ± 6.1	7.8 ± 3.3	0.0012
Two points–ipsilateral			
"Off"	10.6 ± 4.5	8.0 ± 3.8	<0.0001
"On"	9.2 ± 4.9	7.8 ± 5.6	0.0001
Postural stability			
"Off"	1.8 ± 1.0	1.8 ± 1.1	NS
"On"	0.9 ± 0.5	1.0 ± 0.8	NS
Gait			
"Off"	2.3 ± 1.0	2.1 ± 1.2	NS
"On"	0.7 ± 0.6	0.8 ± 0.7	NS
Freezing			
"Off"	2.2 ± 1.3	2.3 ± 1.4	NS
"On"	0.8 ± 1.0	1.2 ± 1.3	NS
Dyskinesia scale score			
Contralateral	2.3 ± 0.7	0.5 ± 0.6	<0.0001
Ipsilateral	2.2 ± 0.7	1.5 ± 0.9	<0.0001
Hoehn and Yahr			
"Off"	4.1 ± 0.4	3.6 ± 0.9	0.0008
"On"	3.0 ± 0.6	2.5 ± 0.8	0.0001
Schwab and England–ADL			
"Off"	52.5 ± 17.7	63.0 ± 18.9	0.01
"On"	78.1 ± 7.9	82.2 ± 9.5	0.023

SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale; ADL = Activities of Daily Living; NS = not significant.

However, of the five patients who could not perform the stand-walk-sit test at baseline, but could at 6 months after pallidotomy, three were still able to do so at their 2-year follow-up. In addition, 10 patients had gait scores that remained significantly ($p = 0.0020$) improved at the 2-year follow-up. The average improvement in these 10 patients was 38%.

In addition to the maintained contralateral benefit at 2 years, we observed significant improvement in ipsilateral dyskinesia, rigidity, and timed tests of motor behavior (see Table 3).

The Schwab and England score and Hoehn and Yahr Staging "on" and "off" also remained significantly improved at the 2-year follow-up. The L-dopa equivalence for the 20 patients followed up for 2 years was 1,028mg, essentially unchanged from a baseline of 1,022mg. Two patients were given tolcapone after their 1-year follow-up. Of the 20 patients followed up for 2 years, 11 were on an L-dopa equivalence dosage that was less than baseline. The average reduction across these patients was 171mg and ranged from as little as 40mg to as much as 480mg.

There was a significant interaction between clinical outcome and age ($r = 0.5$; $p = 0.0008$) with the largest reductions in the total UPDRS occurring in the youngest patients (younger than age 50 years). On average, patients in the youngest group experienced twice the reduction in total UPDRS scores compared with those in the oldest patients (older than age 60 years; Fig 4). Note, however, that even those in the oldest age group experienced a significant reduction in the total UPDRS compared with baseline.

Discussion

Significant improvement in the total UPDRS score and all of the cardinal motor signs of PD was observed for patients undergoing GPi pallidotomy compared with those treated with best medical therapy. Improvement in motor function was greatest on the contralateral side but was also seen on the ipsilateral side for rigidity, bradykinesia, and drug-induced dyskinesias. These benefits were sustained over the 2-year period of follow-up. Compared with another randomized trial of pallidotomy versus best medical therapy,[16] there are several important differences. The previous trial was a multicenter study and did not report follow-up for longer than 6 months. There also was no discussion of the effect of pallidotomy in individual parkinsonian motor signs, and, except for tapping tests, the effect of surgery on contralateral versus ipsilateral symptoms was not compared. Longer follow-up is important because the time at which patients are assessed after surgery may play a significant role in the variability of reported clinical outcome. Some patients may gradually lose part or all of their clinical benefit over time,[8,14,23] particularly if the lesion is not well placed in the sensorimotor portion of GPi.[24,25] Thus, studies with shorter follow-up are more likely to report better outcomes than those with longer follow-up. For example, an earlier study without microelectrode recording reported results similar to those using microelectrode recording at 6 to 12 months follow-up, but by 2 years the patients had largely returned to baseline levels of function.[23]

Although the evaluating neurologist had no contact with the patients between visits and did not participate in the ongoing care of the patients, the profound benefit to the contralateral side with virtual complete abolition of contralateral dyskinesia made the maintenance of a blind study difficult. In this regard, the patients were not blinded to the fact that they had surgery, and one cannot underestimate the contribution of a placebo effect in mediating some of the benefits observed in this study, although the sustained benefit observed in this study would be uncharacteristic of such an effect.

In this study, we found significant benefit in parkinsonian motor signs maintained for 2 years after pallidotomy. These findings are consistent with previous reports by others of sustained long-term benefit after unilateral pallidotomy.[26–28] We also observed a significant ipsilateral benefit at the 2-year follow-up. This is a novel finding because previous studies reported a loss of ipsilateral benefit within the first year after pallidotomy.[8] The lack of data on the effect of pallidotomy on individual parkinsonian motor signs in the previous randomized study is unfortunate, because there remains considerable controversy over the relative effect of pallidotomy on rigidity, bradykinesia, tremor, gait, and balance. For example, one study reported no effect on bradykinesia but a moderate effect on tremor,[10] and another reported little effect on tremor

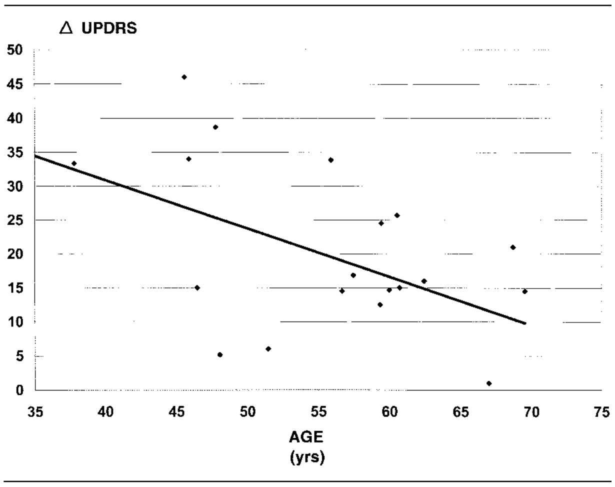

Fig 4. Relationship between change in the total Unified Parkinson's Disease Rating Scale score from baseline to 24 months and age.

but a significant effect on rigidity,[29] whereas others reported improvement in both tremor and akinesia after pallidal lesions.[5–7,30,31] Several studies have, in fact, reported significantly different outcomes after pallidotomy from that reported here.[10–14,29] Sutton and colleagues[11] reported no significant clinical benefit in UPDRS, Schwab and England, or Hoehn and Yahr scores either "on" or "off" after pallidotomy, whereas another reported marked and significant improvement in "on" motor scores.[12] The danger underlying the interpretation of these[10–14,29] and earlier reports in the 1940s to 1960s, in which the outcomes were inconsistent and/or associated with significant morbidity[32–34] lies in the assumption that all the variables that may determine or contribute to clinical outcome were controlled across each of these studies. Clearly they were not.

One factor that is likely to play a major role in determining clinical outcome and that may also account for much of the variability reported across clinical studies is lesion location and size. The internal pallidum is a functionally heterogeneous structure with anatomically and physiologically well-defined motor, associative, and limbic regions. Lesions that involve only a part of or only partially interrupt the outflow of neuronal activity from the motor circuit are less likely to provide optimal long-term relief from parkinsonian motor signs,[24,25,35] whereas those that involve nonmotor circuits are more likely to influence cognitive function.[36,37]

Correlation of lesion location using high-resolution MRIs with clinical outcomes has supported this hypothesis. Lesions that involved the caudal portion of GPi were more effective in providing long-term improvement in parkinsonian motor signs than lesions that only partially involve this territory or involve GPe.[24,25] Furthermore, given the recent description of anatomically segregated pallidothalamocortical "subcircuits" within the larger motor circuit, centered on different precentral motor areas,[38] together with the observation that select motor symptoms may be improved by lesions which involve different portions of the sensorimotor GPi,[35] it is likely that each of these motor subcircuits may be differentially involved in the development of parkinsonian motor signs. Conceivably, in those instances where little or no benefit is reported or some motor signs are reported to improve while others do not, lesions may spare a particular motor subcircuit. Consistent with this proposal, it has been reported that tremor was alleviated to a significantly greater degree with lesions placed more posteriorly in the GPi, whereas rigidity was alleviated with more anteriorly placed lesions.[35] These observations are consistent with the hypothesis that particular portions of the "motor" circuit are preferentially involved in the development of tremor, rigidity, and bradykinesia.

In addition to the location of lesions within GPi, it may also be important to avoid lesioning GPe. Preliminary data in the monkey[39] and more recent work in humans[40] indicate that lesions that involve GPe could limit the benefit of a well-placed lesion in GPi and/or worsen the response to antiparkinsonian medication by minimizing the effect of striatal dopamine. Consistent with these data, the one patient in our cohort who did not improve after pallidotomy had a lesion that included a large part of the posterior portion of GPe. In the study by Sutton and colleagues,[11] in which there was little benefit reported after pallidotomy, the reported lesion size was considerably longer in the dorsal-ventral dimension than the vertical extent of GPi, as seen in the human atlas (Schaltenbrand and Bailey). This suggests that the lesion in some of these cases must have extended outside the borders of GPi, most likely involving GPe, and may account, at least in part, for the lack of benefit seen in these patients. Interestingly, in the one patient who had no improvement in clinical outcome in the study by Krauss and colleauges,[41] the lesion was confined to GPe. Thus, it appears that patients who experienced the most improvement in all symptoms without signs of regression had lesions that encompassed as much of the sensorimotor pallidum as possible without infringing on adjacent structures.[24,25] These data are important because the targeted portion of the pallidum differed in some studies[10,29,42,43] from that targeted by ourselves as well as others[5,6,19,44] and may account for much of the variability in outcomes and for the loss of benefit over time reported in some studies.[23,25] Similarly, the loss of ipsilateral benefit after 6 to 12 months observed in previous studies also may reflect differences in lesion location and/or size.[8,24,25]

The methods used to assess patients, patient selection, and the type and incidence of complications associated with the procedure or which occur subsequently during the time of patient assessment also may contribute to differences observed across studies. For example, in the only study to report significant improvement in "on" motor scores, nonstandardized methods of patient assessment were used to evaluate patients.[42] In other studies, patients with only particular symptoms have been selected[6,7]; in another, the incidence of major complications was exceedingly high (31%, 8 of 26)[14] and was reflected in significant variability in improvement in "off" motor scores ranging from 38% worsening to as much as 54% improvement.

Age is yet another factor that must be taken into consideration when comparing the benefits of pallidotomy. In this study, we observed a clear and significant relationship of age to clinical outcome with younger patients showing significantly more improvement than older patients, independent of disease duration. This is in contrast with reports by others in which no age relationship to clinical outcome was observed,[6,45] but is consistent with the report by Lang and colleagues[8] who reported greater improvement for patients younger than age 65 years versus those older than 65. Our data further suggest that the age relationship is a continuous variable with no apparent threshold effect. Note, however, that even in this study older patients showed substantial benefit after pallidotomy.

The lack of significant improvement in motor or Activities of Daily Living "on" scores observed in this study is consistent with that reported by others,[5,6,8] except in one study.[42] As discussed above, in this study methods and times of patient assessment were not standardized and relied largely on videotape records and patient reports making these data highly subjective and difficult to interpret. Small but significant improvement in the "on" state in the surgical compared with the medical control group were present for the Schwab and England, Hoehn and Yahr, and bradykinesia, gait, and postural stability scores at the 6-month follow-up. Significant improvement in Schwab and England and Hoehn and Yahr "on" scores was still present at 2 years and may reflect the reduction in dyskinesias and motor fluctuations.

This study provides clear evidence that pallidotomy is an effective treatment for the motor symptoms associated with advanced PD and can provide lasting benefit on the cardinal motor features of this disease. A significant lasting benefit on ipsilateral as well as contralateral rigidity, bradykinesia, and drug-induced dyskinesia but not for ipsilateral tremor was observed. In evaluating the results of this and other surgical studies, however, several clinical variables should be taken into account. A greater understanding of the role of these variables in determining clinical outcome will provide important information toward the future application of this and other surgical approaches to the treatment of PD and other movement disorders.

This work was supported by the National Institutes of Health (grant NS 32047, M.R.D.).

We thank J. Ward-Estes and L. Pittman for their valuable help in evaluating patients, J. Stanton for his thoughtfulness and thoroughness in coordinating patient schedules, and R. Miller for her assistance in the preparation of the manuscript.

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