Outcome of unilateral pallidotomy in advanced Parkinson's disease: cohort study of 32 patients

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Abstract

***Objectives*—In a randomised trial to study the efficacy of unilateral pallidotomy in patients with advanced Parkinson's disease, patients having pallidotomy within 1 month after randomisation were compared with patients having pallidotomy 6 months after the primary outcome assessment. Of the 37 patients enrolled 32 had a unilateral pallidotomy. The follow up study of these patients is presented to report (1) clinical outcome; (2) adverse effects; (3) cognitive and behavioural effects; (4) relation between lesion location and outcome; and (5) preoperative patient characteristics predictive for good outcome.**

***Methods*—Outcome measures were the motor section of the unified Parkinson's disease rating scale (UPDRS), levodopa induced dyskinesias, disability, quality of life, and a comprehensive neuropsychological assessment. Multivariate logistic regression was used to identify preoperative patient characteristics independently associated with good outcome.**

***Results*—Off phase assessment showed a reduction in parkinsonism from 49 to 36.5 points on the UPDRS 6 months after surgery. Improvements were also demonstrated for activities of daily living and quality of life. In the on phase dyskinesias were reduced. All effects lasted up to 12 months after surgery. Three patients had major permanent adverse effects. Besides worsening of verbal fluency after left sided surgery, systematic cognitive deterioration was not detected. Patients taking less than 1000 levodopa equivalent units (LEU)/day were more likely to improve.**

***Conclusions*—The positive effects of unilateral pallidotomy are stable up to 1 year after surgery. Patients taking less than 1000 LEU per day were most likely to improve.**

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Patients with advanced Parkinson's disease often face fluctuations between immobility (off phase) and mobility, usually associated with dyskinesias (on phase), despite optimal pharmacological treatment.

The results of several studies indicated that unilateral pallidotomy can improve parkinsonism in the off phase and reduce dyskinesias in the on phase,[1–4] especially on the contralateral body side.[5–10] Important issues, however, such as the optimal lesion location, risks of adverse effects, possible predictive factors for outcome, and consequences for cognition and behaviour need to be sorted out in more detail.[11 12]

We previously published a randomised controlled trial assessing the efficacy of unilateral pallidotomy in patients with advanced Parkinson's disease.[1 13] In the trial patients were randomised to unilateral pallidotomy within 1 month or to postponed pallidotomy 6 months later. In the present paper, we report the follow up study of the patients initially participating in the trial. The study consists of patients with 6 months postoperative assessment and a subgroup of patients with additional assessment 1 year after surgery. The aims of this study were to (1) assess clinical outcome; (2) report on adverse effects; (3) study cognitive and behavioural effects; (4) investigate the relation between lesion location and clinical outcome after 6 months; and (5) investigate possible preoperative patient characteristics predictive of good outcome after 6 months.

Methods

PATIENTS AND STUDY PROFILE

Patients were included in four Dutch hospitals by neurologists whose specialty was movement disorders. The inclusion criteria were (1) idiopathic Parkinson's disease[14] and (2) severe response fluctuations, dyskinesias, painful dystonia, and bradykinesia, despite optimum pharmacological treatment. The exclusion criteria were age below 18 years, Hoehn and Yahr[15] stage 5 at the best moment during the day, a mini mental state examination[16] score of 24 or less, psychosis, and general surgical contraindications (unstable cardiac or pulmonary disease, coagulation disorder).

Thirty seven patients were included in the original trial, of which 19 were randomised to unilateral pallidotomy within 1 month and 18 to postponed pallidotomy, 6 months after the primary outcome assessment.[1] Of the second group five patients had no pallidotomy; two patients died, one had no pallidotomy due to complications after hip surgery, and two patients declined pallidotomy because they had experienced improvement of their situation in the preceding 6 months. Therefore, 32 patients participated in the present study. Nineteen patients were followed up for 12 months after surgery and 13 for 6 months.

The study protocol was approved by the ethics committees of the participating centres and the patients gave their informed consent.

SURGICAL TREATMENT

Surgery took place in three Dutch hospitals. A Leksell stereotactic frame was applied under local anaesthesia or under propofol sedation (three patients). A burr hole was made 2–3 cm lateral from the midline, just anterior to the coronal suture. A positive contrast ventriculography was made for target localisation. The target coordinates for the posteroventral globus pallidus at the border of the medial and lateral segments were 2–3 mm anterior to the midcommissural point, 5 mm below the intercommissural line, and 21–23 mm lateral to the midline of the third ventricle. Microelectrode recordings were not used. Electrical monopolar test stimulation was carried out using an electrode with a 2.1×4.0 mm bare tip. In the trajectory towards the calculated target point, low frequency (2 Hz) and high frequency (100 to 130 Hz) stimulation (pulse width 0.1 ms) was performed in 2 mm steps starting 8 mm above the target. The aim of the stimulation was to determine the proximity of the internal capsule and the optic tract as judged by the clinical effect. With the same electrode, one to four radiofrequency thermolesions were made at 80°C for 60 seconds at each 2 mm step. No lesion was made at a position if low frequency stimulation induced myoclonus below 4 V amplitude, if high frequency stimulation induced dysarthria or paraesthesias, or if the patient had any visual stimulation response with either low frequency or high frequency stimulation.

OUTCOME MEASURES

Clinical outcome

We used the activities of daily living (UPDRS 2) and the motor examination (UPDRS 3) section of the unified Parkinson's disease rating scale,[17] a modified version of the dyskinesia rating scale proposed by Goetz *et al* and Langston *et al*,[18 19] the Barthel index,[20] the Schwab and England scale,[17] and the Parkinson's disease quality of life questionnaire (PDQL).[21] Medication and body weight of the patients were also noted.

Clinical assessment was performed at baseline and after 6 and 12 months in defined "off" and "on" phases. The dyskinesia rating scale and the PDQL were rated in the on phase only. The off phase was defined as the condition of the patient after withholding antiparkinson medication for 12 hours and being awake for at least 1 hour. The on phase was the condition 1 hour after taking the usual first morning dose. All patients were assessed on clinical rating scales by the same assessor.

Several items of the UPDRS 3, for each side of the body, were combined to assess the effect on separate symptoms: tremor=arm and leg rest tremor and arm action tremor (scores 20+21); akinesia=finger taps, hand movements, rapid alternating movements of the hand, and leg agility (scores 23+24+25+26); rigidity=arm and leg rigidity (score 22); postural instability/gait disorder (PIGD)= posture, gait, and postural stability (scores 28+29+30).

For the dyskinesia rating scale the physician watched the patient putting on and buttoning a coat, drinking from a cup, and walking. Dyskinesias of each limb, the head and the trunk were rated according to the following score: 0=absent; 1=minimal severity, no interference with voluntary motor acts; 2=dyskinesias may impair voluntary movements but patient is normally capable of undertaking most motor acts; 3=intense interference with movement and daily activities are greatly limited; 4=violent dyskinesias, incompatible with normal motor task.

The PDQL questionnaire consists of four subscales: Parkinson, systemic, emotional, and social. The questionnaire was administered in the on phase, but patients were asked to rate their perceived quality of life irrespective of off and on phases.

To analyse changes in pharmacological treatment, we pooled different drugs in levodopa equivalent units (LEU) according to the conversion formula: 100 LEU=100 mg regular levodopa, given with a peripheral decarboxylase inhibitor (PDI)=133 mg levodopa (+PDI) in controlled release tablets=10 mg bromocriptine=1 mg pergolide mesylate.

Adverse effects

Adverse effects were recorded by a neurologist 1 week after the pallidotomy and at the 6 and 12 month assessments, using a structured list of possible complications.

Cognitive and behavioural effects

Neuropsychological examination was conducted as much as possible while patients were at their best. The examination was suspended whenever a patient indicated that he or she went into an immobile phase, or whenever dyskinesias were interfering with test administration. Duration of the examination was 3 hours. The tests were administered or supervised by a board certified neuropsychologist. The examination was done at baseline, at 6 months, and at 12 months follow up.

Relation between lesion location and clinical outcome

Magnetic resonance imaging was planned at least 3 months after the pallidotomy. Each lesion was visually evaluated (RMAB and JDS) on the MRI for location and extension in relation to the globus pallidus internus (GPi), globus pallidus externus (GPe), putamen, and internal capsule (IC). Additionally, we recorded possible infarcts or haemorrhages. Clinical outcomes were the change in UPDRS off phase score (preoperative minus 6 months postoperative score) and the neuropsychological test scores.

Preoperative patient characteristics predictive for good outcome

We analysed the impact of preoperative age, off phase Hoehn and Yahr stage, off phase UPDRS 3 score, on phase UPDRS 3 score, levodopa effect, medication in LEU, and side of surgery on good outcome 6 months after

Table 1 Baseline characteristics, 32 patients

Sex: men/women (No of patients)	16/16
Mean age (y (SD))	60.6 (7.2)
Mean age of disease onset (y (SD))	44.4 (9.2)
Median Hoehn and Yahr stage off/on (range)	4 (2–5)/2.5 (1–4)
Side of surgery: right/left (No of patients)	22/10
Mean medication (LEU (SD))	961 (433)

LEU=Levodopa equivalent units.

pallidotomy. Continuous variables were dichotomised at a predetermined score. A good outcome was defined as an improvement of more than 10 points on the UPDRS 3 in the off phase (UPDRS 3 preoperative minus 6 months postoperative score).

STATISTICAL ANALYSIS

Changes in clinical assessment data were analysed with the non-parametric Wilcoxon signed rank test and the Friedman's test. Changes in body weight and medication were analysed with the paired samples *t* test.

For analysis of the neuropsychological test results the sample was divided into left sided and right sided pallidotomy subgroups, because many of the tests measure lateralised cerebral functions. Changes in cognitive functioning were tested using the Wilcoxon signed rank test. Subgroup differences in change scores (change score=6 months postoperative minus preoperative score) were tested with the Mann-Whitney *U* test.

Three per cent of the neuropsychological test scores were missing, mostly due to prolonged off phases. These missing data were dealt with as follows. At baseline a missing value was replaced by the worst value seen in the patient group when a patient had attempted a test but was unable to do it. If the test was not administered, the missing value was estimated on the basis of its main correlate (a missing score of trailmaking B was estimated using the score obtained at trailmaking A). Missing values at one of the follow up periods were either replaced by the worst value seen in the patient group when the patient had attempted to do the test or else by the value obtained at the previous assessment.

To identify preoperative patient characteristics associated with good outcome 6 months after pallidotomy, the χ^2 test or the Fisher's exact test was used when numbers were small. Additionally, as it was expected that characteristics of patients were interrelated, we analysed the factors with multivariate logistic regression. Characteristics with $p \leqslant 0.50$, identified from univariate analysis, were forced into the logistic model. The effect sizes were expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). Calibration of the regression model was assessed with the Hosmer-Lemeshow goodness of fit test. This test compares observed and expected frequencies of the outcome in groups based on the values of the estimated probabilities, using the logistic model. In this test, a high p value indicates that the model is performing well—that is, that there is not a large discrepancy between observed and expected outcome.

In view of the explorative nature of this study, no statistical adjustments for multiple comparisons were made.[22]

Results

PARTICIPANT FLOW AND FOLLOW UP

Table 1 shows the baseline characteristics.

Of the 19 patients with 12 months follow up, one patient refused follow up assessment in the defined off phase (other outcome measures were obtained) and one patient could not be scored for the 12 months assessment due to unrelated disease.

Of the 13 patients with 6 months follow up, one had an intracerebral haemorrhage directly after surgery and became hemiplegic. Because most rating scales are Parkinson's disease specific and the standardised assessment was considered too stressful for this patient, we did not perform the follow up assessment in this patient.

CLINICAL OUTCOME

Off phase assessment

In the standardised off phase the median UPDRS 3 score was reduced from 49 to 36.5 points 6 months after unilateral pallidotomy ($p<0.001$; table 2). Tremor, akinesia, and rigidity contralateral to the side of pallidotomy were improved ($p<0.001$). The ipsilateral symptoms did not change after pallidotomy, except for a slight improvement in akinesia ($p=0.02$). Postural instability was improved 1.5 points 6 months after pallidotomy ($p=0.002$).

Table 2 Median (range) scores on clinical outcome scales in standardised off phase

Measure	*Best score/worst score*	*Preoperative (n=30)*	*6 months postoperative (n=30)*	*p Value**	*12 months postoperative (n=17)*	*p-value†*
UPDRS 3	0/108	49 (19–91)	36.5 (11–66)	<0.001	37 (17–71)	<0.001
Tremor contralateral	0/12	4 (0–9)	0 (0–8)	<0.001	0 (0–3)	0.001
Tremor ipsilateral	0/12	1 (0–7)	0 (0–9)	0.16	2 (0–7)	0.06
Akinesia contralateral	0/16	12 (4–16)	7 (0–14)	<0.001	7 (2–16)	0.001
Akinesia ipsilateral	0/16	9 (0–15)	8 (1–15)	0.02	7 (2–16)	0.15
Rigidity contralateral	0/8	4 (1–8)	2 (0–7)	<0.001	2 (0–5)	<0.001
Rigidity ipsilateral	0/8	2 (1–8)	2 (0–8)	0.06	2 (0–4)	0.24
PIGD	0/12	6.5 (0–12)	5 (0–12)	0.002	5 (1–12)	0.03
UPDRS 2	0/52	30 (11–46)	23.5 (8–42)	<0.001	23 (14–42)	0.04
Barthel index	20/0	10 (4–20)	15 (4–20)	<0.001	17 (4–20)	0.02
SE scale	100/0	30 (10–80)	60 (20–90)	<0.001	50 (10–90)	0.01

UPDRS=Unified Parkinson's disease rating scale; PIGD=postural instabilty and gait disturbances; SE scale=Schwab and England scale.
*Data compared with preoperative data (Wilcoxon signed ranks test).
†Data compared with preoperative and 6 months postoperative data (Friedman test).

Table 3 Median (range) scores on clinical outcome scales in standardised on phase

Measure	*Best score/ worst score*	*Preoperative (n=31)*	*6 months postoperative (n=31)*	*p Value**	*12 months postoperative (n=18)*	*p-value†*
UPDRS 3	0/108	19.5 (1–78)	20 (2–54)	0.54	25 (3–45)	0.67
Tremor contralateral	0/12	0 (0–6)	0 (0–6)	0.30	0 (0–1)	0.09
Tremor ipsilateral	0/12	0 (0–5)	0 (0–5)	0.23	0 (0–5)	0.95
Akinesia contralateral	0/16	6 (0–14)	6 (0–14)	0.81	5.5 (2–14)	0.90
Akinesia ipsilateral	0/16	4.5 (0–14)	5 (0–11)	0.98	4.5 (0–10)	0.82
Rigidity contralateral	0/8	1 (0–7)	1 (0–4)	0.15	1 (0–3)	0.31
Rigidity ipsilateral	0/8	0.5 (0–8)	1 (0–4)	0.96	0.5 (0–6)	0.82
PIGD	0/12	3 (0–11)	2 (0–10)	0.23	3 (0–12)	0.02
DRS	0/24	7.5 (0–21)	2 (0–8)	<0.001	2.5 (0–13)	0.01
DRS contralateral	0/8	3.5 (0–8)	0 (0–3)	<0.001	0 (0–5)	<0.001
DRS ipsilateral	0/8	2 (0–8)	2 (0–5)	0.37	1.5 (0–5)	1.0
UPDRS 2	0/52	12 (4–26)	12 (4–26)	0.32	11 (5–21)	0.94
Barthel index	0/20	20 (11–20)	19 (12–20)	0.92	19.5 (7–20)	0.72
SE scale	100/0	80 (30–90)	80 (50–100)	0.22	85 (30–90)	0.26
PDQL	185/37	111 (61–141)	88 (43–163)	<0.001	95.5 (48–142)	0.03

UPDRS=Unified Parkinson's disease rating scale; PIGD=postural instabilty and gait disturbances; DRS=dyskinesia rating scale; SE scale=Schwab and England scale; PDQL=Parkinson's disease quality of life questionnaire.
*Data compared with preoperative data (Wilcoxon signed ranks test).
†Data compared with preoperative and six months postoperative data (Friedman test).

These effects lasted up to 12 months after surgery (table 2).

For activities of daily living (ADL), improvements could be demonstrated on the UPDRS 2, the Barthel index, and the Schwab and England scale 6 months after pallidotomy (p<0.001), lasting up to 12 months (table 2).

On phase assessment

Six months after surgery the median score on the total dyskinesia rating scale was reduced from 7.5 to 2 points (p<0.001). The effect could only be demonstrated on the contralateral body side (from 3.5 to 0; p<0.001) and was sustained 12 months after surgery (table 3).

The total UPDRS 3 and its subscores, the UPDRS 2, the Barthel index, and the Schwab and England scale did not change in the on phase (table 3).

The PDQL improved from 111 to 88 points (p<0.001) 6 months after pallidotomy and was still improved 12 months after surgery (table 3). This improvement consisted of an improvement on all physical and psychosocial subscales.

In the first 6 months, the mean body weight increased from 67.6 kg to 71.6 kg (p<0.001; n=31). The body weight was 70.9 kg 12 months after surgery (p=0.15 compared with baseline; n=18). There were no significant changes in the use of medication; patients used 963 LEU before surgery, 1040 LEU at 6 months follow up, and 954 LEU at 12 months follow up.

ADVERSE EFFECTS

The adverse effects are shown in table 4. Altogether, 17 patients had adverse effects, permanent in 14. The most frequent adverse effects were facial paresis and drooling. Three patients had major adverse effects. In one patient dysarthria started directly postoperatively, followed by reduced consciousness for a few hours, and a pseudobulbar syndrome. Six months after surgery he still had dysphasia, drooling, and postural instability, the last two symptoms were still present 12 months after surgery. On MRI the lesion was situated in the GPi and GPe and extended into the internal capsule. A second patient had an intracerebral haemorrhage directly postoperatively, which was evacuated 4 hours later. Six months after surgery the patient had a left sided hemiparesis and neglect. He was severely disabled. In another patient surgery had to be discontinued, due to psychosis after sedation with propofol, which was given for fixation of the

Table 4 Adverse effects in 32 patients

Patient	*One week after surgery (32 evaluated)*	*Six months after surgery (32 evaluated)*	*12 months after surgery (19 evaluated)*
1	Dysarthria, reduced consciousness for a few hours, pseudobulbar syndrome	Dysphasia, drooling and postural instability	Drooling and postural instability
2	During surgery confused, surgery not completed	Intermittent hallucinations / psychosis	Intermittent hallucinations / psychosis
3	Hiccups	Loss of concentration	Loss of concentration
4	Urinary incontinence	Urinary incontinence	Urinary incontinence
5	Facial paresis	Facial paresis, drooling	Facial paresis, drooling
6	Reduced speech volume	Facial paresis, drooling, fatigue	None
7	Dysarthria, starting some days after surgery	None	None
8	Severe headache while supine starting 4 days after surgery, lasting a few days	None	None
9	Urinary incontinence	None	None
10	Intracerebral haematoma, evacuated surgically	Hemiparesis, neglect, and severely disabled	
11	Postural instability for 6 days, dysphasia, facial paresis	Dysphasia (predominantly expressive), impaired coordination while swimming	
12	Facial paresis, word finding difficulties starting 2 days after surgery	Facial paresis, word finding difficulties	
13+14	Facial paresis	Facial paresis, drooling	
15	None	Sexual disinihibition, increased libido	
16	None	Painful skin while combing	
17	None	Drooling	

Table 5 Mean (SD) preoperative scores and 6 months postoperative change scores on neuropsychological tests. Descriptions of these tests can be found in Schmand et al[13]

	Right pallidotomy (n=20)		Left pallidotomy (n=9)	
	Preoperative score	Change score	Preoperative score	Change score
Boston naming test	52.1 (8.1)	−0.6 (2.5)	52.4 (7.7)	0.2 (2.8)
Category fluency	37.1 (12.9)	−2.8 (8.4)	36.7 (7.7)	−8.3 (4.6)**†
Letter fluency COWAT	33.1 (13.7)	0.5 (5.8)	34.3 (15.0)	−7.6 (10.6)*
WAIS similarities (T)	60.5 (15.4)	−0.4 (6.7)	57.6 (14.8)	1.1 (5.9)
WAIS block design (T)	46.3 (14.5)	−1.3 (10.3)	42.8 (11.2)	−0.7 (7.3)
Bells test left 2 columns	8.2 (2.0)	−0.1 (1.9)	9.1 (0.8)	0.0 (1.0)
Bells test right 2 columns	8.3 (1.7)	0.1 (1.7)	9.3 (1.1)	−0.2 (1.0)
Bells test time (s)	135 (54)	4 (39)	107 (29)	37 (36)*†
JOLO	22.4 (7.1)	−1.5 (5.5)	25.0 (5.4)	−1.0 (6.0)
Rey AVLT total	36.8 (10.7)	1.9 (7.7)	36.4 (12.8)	−0.7 (9.5)
Rey AVLT delayed recall	7.1 (3.1)	0.6 (2.2)	8.2 (3.7)	−0.6 (3.2)
Rey AVLT recognition	27.9 (2.6)	−1.0 (2.0)*	27.0 (3.7)	0.6 (2.6)
Logical memory immediate§	8.1 (3.2)	1.5 (3.8)	8.0 (2.7)	0.1 (3.6)
Logical memory delayed§	7.1 (2.8)	1.5 (3.7)	7.6 (2.8)	−0.3 (2.9)
Recognition faces	39.1 (6.4)	0.0 (4.1)	38.7 (6.5)	−0.4 (3.7)
Trailmaking A (s)	77 (75)	0 (25)	57 (21)	8.8 (26)
Trailmaking B (s)	164 (115)	4 (51)	161 (76)	18 (59)
Stroop words (s)	67 (61)	−4 (11)**	55 (8)	5 (6)‡
Stroop colours (s)	88 (109)	0 (12)	65 (13)	9 (12)†
Stroop colour-words (s)	154 (159)	2 (29)	143 (61)	9 (48)
Stroop-Bohnen	195 (198)	15 (58)	205 (60)	−3 (63)
MWCST errors	16.0 (9.1)	0.0 (6.9)	13.3 (7.3)	3.9 (9.9)
MWCST perseverations	5.8 (4.8)	−1.6 (4.7)	3.8 (2.9)	2.0 (3.3)†
MWCST categories	4.1 (1.7)	−0.2 (1.3)	3.6 (1.8)	−0.6 (2.0)

*p<0.05; **p<0.01 Wilcoxon signed ranks test of pre−post difference; †p<0.05; ‡p<0.01 Mann-Whitney *U* test of group differences in change score.

Change score=6 months postoperative minus preoperative score; § Logical memory of the Rivermead behavioural memory test; COWAT=controlled oral word association test; WAIS=Wechsler adult intelligence scale; JOLO=judgement of line orientation, age and sex corrected scores; AVLT=auditory verbal learning test; MWCST= modified Wisconsin card sorting test; T=age corrected T score.
Negative change scores indicate decline in performance except for MWCST errors, MWCST perseverations, and test variables expressed in seconds.

frame. One lesion was made. The patient was admitted to a psychiatric hospital and remained intermittently psychotic. He had an episode of depression before inclusion in the study. There was no lesion visible on MRI.

COGNITIVE AND BEHAVIOURAL EFFECTS

The left and right sided subgroups were similar in sex, age, educational level, premorbid verbal intelligence, and medication use (benzodiazepines, anticholinergic agents, and LEU). There was one left handed patient in each of the subgroups.

The neuropsychological test scores are shown in table 5. The table provides the mean preoperative score and the mean change score (change score=postoperative minus 6 months preoperative score) for each test variable. None of the preoperative test scores showed a significant difference between the left and right sided pallidotomy subgroups.

Table 6 Lesion location in relation to UPDRS 3 off phase change scores (preoperative minus 6 months postoperative score)

		Preoperative UPDRS 3 off phase score		Change score	
Lesion location	Patients	Score	Range	Score	Range
GPi	2	44.5	24/65	15	6/24
GPe	2	43	42/44	19	15/23
Putamen	1	19	—	8	—
GPi and GPe	11	56	38/81	19	1/32
GPi, GPe, and putamen	2	72	53/91	23.5	15/32
GPe and putamen	1	43	—	18	—
GPi, GPe, and IC	1	47	—	−13	—
No lesion visible	4	51	44/63	18	7/27

GPi=Internal segment of the globus pallidus; GPe=external segment of the globus pallidus; IC=internal capsule; minus sign indicates deterioration.

After the operation the left sided pallidotomy subgroup scored significantly less at both category fluency and letter fluency. The speed of performance on the Bell's test also slowed down in the left sided pallidotomy patients. The right sided subgroup recognised slightly less words postoperatively at the auditory verbal memory test. At follow up they were slightly faster in the word reading condition of the Stroop test, whereas the left sided subgroup tended to be slower. A similar pattern was found in the colour naming condition of the Stroop test. After the operation the patients with right sided pallidotomy perseverated slightly less at the modified Wisconsin card sorting test whereas the patients with left pallidotomy perseverated slightly more. The within group changes were not significant, but the postoperative difference between the groups was. In the remaining cognitive tests no significant changes over time or subgroup differences in change scores were found.

RELATION BETWEEN LESION LOCATION AND CLINICAL OUTCOME

In 24 patients MR images were obtained between 1.8 and 18.5 months after pallidotomy (median 7.3 months; one patient <3 months). The lesion location and the change in UPDRS 3 off phase score after pallidotomy are shown in table 6. In eight patients we did not detect a lesion in the GPi, although these patients improved a median of 18 points. In four of these patients the lesion was situated outside the GPi and in the other four we did not discern a lesion. There was also no discernible pattern of associations between the location of the lesion or the number of lesioned structures as found on MRI and changes in the neuropsychological test scores.

PREOPERATIVE PATIENT CHARACTERISTICS PREDICTIVE FOR GOOD OUTCOME

Table 7 shows the univariate relations between preoperative patient characteristics and good outcome. Medication of 1000 or less LEU/day was associated with a good outcome (p=0.05). Age, on phase UPDRS 3 score, medication, and side of surgery (p≤0.50) were entered into the multivariate logistic model. The results showed that medication of 1000 or less LEU (OR 9.1; p=0.03) was the only variable independently associated with good outcome 6 months after pallidotomy (table 8).

Discussion

CLINICAL OUTCOME

Off phase assessment

Our study showed an improvement of parkinsonism in the off phase of 25%, measured with the UPDRS 3. Six and 12 months after surgery, tremor, akinesia, and rigidity were improved on the contralateral body side. In addition, we found that functioning in activities of daily living was improved after pallidotomy up to 1 year.

The results concerning the effect of pallidotomy on akinesia in the off phase, shown by several studies, are varying, but most studies do

Table 7 Preoperative patient characteristics in relation to good outcome 6 months after pallidotomy (n=30)

*Characteristic of patients**	*Poor UPDRS 3 change score† ≤10*	*Good UPDRS 3 change score†>0*	*p Value‡*
Age:			
≥65 y	4	6	0.43
<65 y	5	15	
Hoehn and Yahr stage in off phase:			
>3	6	14	1
≤3	3	7	
UPDRS 3 in off phase:			
≥50	4	12	0.69
<50	5	9	
UPDRS 3 in on phase:			
>15	5	15	0.43
≤15	4	6	
Levodopa effect on UPDRS 3 score:			
<30	6	11	0.69
≥30	3	10	
Medication:			
>1000 LEU	7	7	0.05
≤1000 LEU	2	14	
Side of surgery:			
Right	7	13	0.34
Left	2	8	

*Continuous variables were dichotomised at a predetermined score.
†Change score=preoperative minus 6 month postoperative score.
‡Differences between frequencies were analysed with χ^2 tests or the Fisher's exact test when numbers were small.

show an improvement.[5–7 9 10 23] Johansson *et al*[24] found no effect on akinesia, but they did not assess patients in standardised off and on phases.

The current study demonstrated a slight — but statistically significant — effect on postural instability and gait disturbances (PIGD) up to 1 year after surgery. Others found the same initial effect on PIGD,[6 7 9 25–27] however, in some studies the effect disappeared gradually.[5 28]

ON PHASE ASSESSMENT

The most impressive effect of pallidotomy is the reduction of dyskinesias, most clearly on the contralateral body side.[5 7 10] Our study demonstrated a contralateral effect up to 1 year after surgery. We did not find an ipsilateral dyskinesia effect, although, Samuel *et al*[7] found an improvement of ipsilateral dyskinesias 3 months after surgery, which had disappeared 9 months later.[29] The improvement of dyskinesias, together with the unaltered severity of parkinsonism (according to the UPDRS 3 score), did not result in an amelioration of functioning in activities of daily living in the on phase.

Six months after surgery, we found a clear improvement of the perceived quality of life, which remained significant up to 12 months after surgery. Although the PDQL questionnaire was administered in the on phase, patients were asked to rate their perceived quality of life irrespective of off and on. The improved off phase symptomatology and the reduction of dyskinesias, together with the improved functioning in activities of daily living, could explain the effects on the perceived quality of life.

The mean body weight increased. Weight increase after pallidotomy[2 7 30] and after electrical stimulation of the nucleus subthalamicus[31] has been reported before.

Table 8 Preoperative patient characteristics in relation to good outcome 6 months after pallidotomy: logistic regression model (n=30)

	Improvement >10 on UPDRS 3 in off phase		
	*Adjusted odds ratio**	*95% CI*	*p Value†*
Age <65 y	4.5	0.5–38.6	0.17
UPDRS 3 in on phase>15	2.0	0.3–13.8	0.48
Medication in LEU≤1000	9.1	1.2–70.8	0.03
Side of surgery: right side	0.4	0.04–3.3	0.37

*Reference group are patients with the opposite characteristics.
†Calculated with Wald statistics.
Hosmer-Lemeshow goodness of fit test, p=0.62.

ADVERSE EFFECTS

In our study, three of the 32 patients operated on had only transient and 11 had permanent minor adverse effects. This is in agreement with other reports, in which transient adverse effects vary between 5% and 60% and permanent effects between 0 and 40%.[5–9 24–26]

Three patients had major permanent adverse effects. One of the patients became psychotic after the discontinuation of the propofol sedation before the lesion was made. We consider the impact of the experience in the operating room, frame fixation to the head, and being off medication, so frightful for the patient that this precipitated the psychosis, instead of the small pallidotomy lesion. In one patient, the lesion encroached on the internal capsule, and caused severe adverse effects. It is possible that microelectrode recordings for lesion placement reduce the risk of harming the internal capsule, although groups using microelectrode recordings have reported this complication too.[8 32] The extension of the lesion into the internal capsule could also be due to infarction. The necessity of microelectrode recordings for adequate, safe procedures is still controversial.[11 12 33] Microelectrode recordings are technically very demanding for the clinical setting and lengthen the procedure considerably. Another patient had an intracerebral haemorrhage. In previous studies on pallidotomy, frequencies of infarcts and intracerebral bleeding ranged from 0% to 20%.[5–9 24–26] As functional stereotactic neurosurgery in Parkinson's disease is not without risk, even in experienced hands, we think that the indication for pallidotomy should be restricted to patients with advanced disease, who are still mobile at their best moment during the day.

COGNITIVE AND BEHAVIOURAL EFFECTS

The neuropsychological test results confirmed the findings of our initial trial.[13] As before, the main finding was a decrease in verbal fluency after left sided pallidotomy. This seems to be a permanent effect, as it was still present 1 year after surgery in the patients with left sided pallidotomy (data not shown). A reduction of verbal fluency has been found in several studies as an effect of both pallidotomy and pallidal stimulation.[34–36]

The results on the MWCST suggest some impairment of mental flexibility in the left sided group. This effect is small and not seen in other tests of executive functioning (Stroop test and trailmaking).

The sample size of this study, however, was too small to rule out the possibility of

infrequent but clinically important cognitive and behavioural side effects.

RELATION BETWEEN LESION LOCATION AND CLINICAL OUTCOME

The optimal location and size of the lesions within the globus pallidus are unknown. The model proposed by Alexander and Crutcher[37] predicts improvement of parkinsonian symptoms and an increase of dyskinesias following destruction of the GPi, and many authors state that they try to make the lesion in the Gpi.[3–5] Others prefer to make the lesion in the posteroventral pallidum on the border of the internal an external segments.[38] There were variations in the location of our visible lesions. In four patients we did not detect a lesion at all on MRI, although these patients improved 18 points on the off phase UPDRS 3. In another four cases the lesion was situated outside the GPi. Although the conclusion that it is not necessary to lesion a part of the GPi cannot be drawn from these results, because resolution may have influenced our findings, this finding suggests that a small lesion, even partly in the GPi, may be sufficient to improve symptoms.

PREOPERATIVE PATIENT CHARACTERISTICS PREDICTIVE FOR GOOD OUTCOME

Predictive factors for reduction of dyskinesia could not be established because contralateral dyskinesias are clearly diminished in almost all patents. In our study, 22 of the 31 evaluated patients scored preoperatively two or more points for contralateral dyskinesias, whereas only one patient had a score higher than one point postoperatively.

As a possible predictor of reduction in off phase parkinsonism, we found that patients taking 1000 LEU or less were more likely to have a good outcome than patients taking more than 1000 LEU.

We could not find an association between preoperative off phase Hoehn and Yahr stages, UPDRS 3 off phase scores, or preoperative levodopa response on the UPDRS 3 scores and good outcome. Our sample size, however, was not large enough to exclude the existence of important associations. Samuel *et al*[7] found a significant correlation between magnitude of preoperative levodopa response and clinical outcome. Baron *et al*[25] showed that age was inversely related to postoperative improvement in total UPDRS scores, whereas the study of Kishore *et al*[9] showed the opposite; older patients tended to show greater improvement. Our results and the results of other studies supported neither of these hypotheses.[3 26 39]

Conclusion

Unilateral pallidotomy in advanced Parkinson's disease improves parkinsonism in the off phase and reduces dyskinesias in the on phase. The effects are stable up to 1 year after surgery. Unilateral pallidotomy also leads to an improved functional health and perceived quality of life. Other than reduction of verbal fluency after left sided surgery, we did not detect systematic cognitive deterioration after pallidotomy. We found no relation between age or levodopa response and outcome of surgery, but patients taking less than 1000 levodopa equivalent units/day are most likely to improve.

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Appendix

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