Stereotactic pallidotomy in Parkinson's disease

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Chapter 3

Unilateral pallidotomy in Parkinson's disease: a randomised, single-blind, multicentre trial

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Summary

Background The results of several cohort studies suggest that patients with advanced Parkinson´s disease would benefit from unilateral pallidotomy. We have assessed the efficacy of unilateral pallidotomy in a randomised, single-blind, multicentre trial.

Methods We enrolled 37 patients with advanced Parkinson's disease who had, despite optimal pharmacological treatment, at least one of the following symptoms: severe response fluctuations, dyskinesias, painful dystonias, or bradykinesia. Patients were randomly assigned to unilateral pallidotomy within 1 month or to pallidotomy after the primary outcome assessment (6 months later). The primary outcome was the difference between the groups in median changes on the motor examination section of the unified Parkinson´s disease rating scale (UPDRS motor) score done in the off phase. Secondary outcome measures included levodopa-induced dyskinesias (dyskinesia rating scale [DRS]) and extent of disability (UPDRS activities of daily living).

Findings The median UPDRS motor off score of the pallidotomy patients improved from 47 to 32.5, whereas that of control patients slightly worsened from 52.5 to 56.5 ($p<0.001$). In the on phase the median DRS score improved 50 percent in pallidotomy patients compared to no change in controls. The UPDRS activities of daily living off score improved with a median of 7 in the pallidotomy group. Two treated patients had major adverse effects.

Interpretation Unilateral pallidotomy is an effective treatment in patients with advanced Parkinson's disease, who have an unsatisfactory response to pharmacological treatment.

Introduction

Patients with advanced Parkinson's disease frequently show rapid, seemingly unpredictable, swings between mobility ('on' phase), usually with dyskinesias, and immobility ('off' phase). Many of these patients respond unsatisfactorily to adjustments of the pharmacological treatment.

Cohort studies suggest that unilateral pallidotomy in patients with advanced Parkinson's disease can improve parkinsonism in the off phase and dyskinesias in the on phase.[1-10] We did a randomised controlled trial to assess the efficacy of unilateral pallidotomy in patients with advanced Parkinson's disease. The primary aim was to investigate the effects of unilateral pallidotomy on motor symptoms and signs of Parkinson's disease. Secondary objectives included assessment of effects on levodopa induced dyskinesias, degree of disability, and perceived quality of life. In addition, we recorded adverse effects and changes in pharmacological treatment. The protocol also included a comprehensive neuropsychological assessment, which will be reported elsewhere.

Methods

Patients Patients were recruited from four Dutch hospitals between May, 1997, and May, 1998. Neurologists whose specialty was movement disorders included patients if they had idiopathic Parkinson's disease[11] and, despite optimal pharmacological treatment, at least one of the following symptoms: severe response fluctuations, dyskinesias, painful dystonias, or bradykinesia. Exclusion criteria were: age below 18 years, Hoehn and Yahr[12] stage 5 at the best moment during the day, a mini mental state examination[13] score of 24 or less, psychosis, and contraindications for stereotactic neurosurgery such as a physical disorder making surgery hazardous (severe hypertension, blood coagulation disorder, severe dysphagia, or dysphasia). The study protocol was approved by the ethics committees of the participating centres. Patients received written information about the study and gave their informed consent. Before baseline assessment, we recorded sex, age, age at onset of Parkinson's disease, Hoehn and Yahr stage, and medication use.

Design Patients were randomised to unilateral pallidotomy within 1 month, which we call the pallidotomy group, or to pallidotomy after the primary outcome assessment, 6 months later (control group). Changes in pharmacological treatment were allowed in both groups.

After inclusion and baseline assessment, the neurologist at the treatment centre faxed the necessary data for randomisation to the Department of Biostatistics and Clinical Epidemiology at the Academic Medical Center, Amsterdam. Patients were allocated randomly by a computer program. A minimisation procedure[14]

was done according to severity of Parkinson's disease (Hoehn and Yahr stage < 4 versus Hoehn and Yahr stage 4 or 5 in the off phase) and treatment centre. The minimisation procedure concentrates on minimising imbalance in the distributions of treatment numbers within the various values of each individual possible prognostic factor.[14] All analyses were done separately for the patients staged Hoehn and Yahr below 4 and the patients who were Hoehn and Yahr stages 4 or 5 in the off phase. Since these showed the same results, we present the results of the total treatment groups only.

All patients were assessed on clinical rating scales by the same assessor, who was unaware of the treatment allocation. The patients were instructed not to tell the assessor the treatment they received. Before assessment, a nurse provided bald patients with a headcap to conceal the presence or absence of a pallidotomy scar. Patients assigned to pallidotomy within 1 months did not receive antiparkinsonism drugs on the day of surgery until the end of the procedure. The Leksell stereotactic frame was applied under local anaesthesia (centres 1 and 3) or under propofol sedation (centre 2). A burr hole with a diameter of 10 mm was made 2-3 cm lateral from the midline just anterior to the coronal suture. For target localisation, a positive-contrast ventriculography was done. The target coordinates were 2 mm anterior to the midcommissural point, 5 mm below the intercommissural line and 22 mm lateral to the midline of the third ventricle. Microelectrode recording was not done. Electrical monopolar test stimulation was done with an electrode with a 2.1 x 4.0 mm bare tip with low-frequency (2 Hz) and high-frequency (100-130 Hz) stimulation (pulse width 0.1 ms) 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. If necessary, the target structure was adjusted. Radio frequency thermolesions were made with the same electrode at 80°C for 60 s at each 2 mm step directly after stimulation.

Baseline and 6-month assessments were done in standardised off and on phases. The off phase was defined as the condition of the patient after withholding antiparkinsonism medication for 12 h and being awake for at least 1 h. The on phase was the condition 1 h after the usual first morning dose.

The primary outcome was the difference between the pallidotomy group and the control group in median change scores (change score = difference between baseline and 6-month assessment score) of the motor examination section of the unified Parkinson´s disease rating scale[15] (UPDRS motor) done in defined off phase (table 1). Secondary outcome measures included clinical rating scales (table 1), timed tests, patients' diaries and recording of pharmacological treatment. The clinical rating scales consisted of the UPDRS motor examination section (on phase), the dyskinesia rating scale proposed by Goetz and colleagues,[16,17] a visual analog scale (VAS) for pain,[18] the Barthel Index,[19,20] the UPDRS activities of daily living section,[15] the Schwab and England scale,[15] and the Parkinson´s disease

Table 1. Clinical rating scales

Clinical rating scales	Domain	Best score	Worst score	Phase
Primary outcome				
UPDRS 3	Parkinsonism	0	108	Off
Secondary outcome				
UPDRS 3	Parkinsonism	0	108	On
Dyskinesia rating scale	Dyskinesias	0	4	On
Pain VAS (mm)	Pain	0	100	Off/on
Barthel Index	Disability in ADL	20	0	Off/on
UPDRS 2	Disability in ADL	0	52	Off/on
SE scale	Disability in ADL	100	0	Off/on
PDQL*	Perceived quality of life	185	37	On†

ADL=activities of daily living; * The PDQL consists of the following 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.

quality of life questionnaire[21] (PDQL, table 1). The tapping test and the stand-walk-sit test — timed tests recommended by the core assessment program for intracerebral transplantations committee[17,22] — were part of the assessment protocol and were done in the off and the on phases.

Patients completed two diaries before baseline assessment. In each diary they rated every period of 30 min from 0600 h to 2400 h for 7 days. The first diary recorded symptoms. Patients rated periods of 30 min as: asleep, parkinsonism, on without dyskinesias, or on with dyskinesias. The second diary focused on functioning in activities of daily living. Patients rated asleep, help needed with all activities of daily living, help needed with some activities of daily living, or independent. A score was calculated for each individual diary rating. For example, the periods rated as parkinsonism were counted. The subsequent sum score was divided by 14 ([60 min/30 min] x 7 days), giving a score equivalent to h per day. Patients completed the same two diaries at the time of the 6-month assessment.

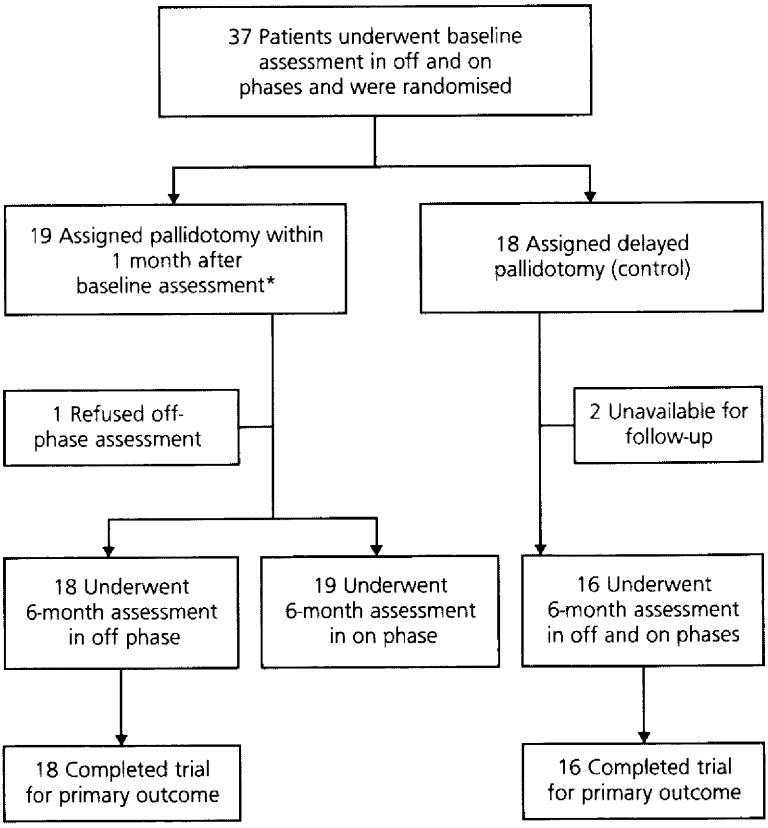
To analyse changes in pharmacological treatment, we pooled different drugs in levodopa equivalent units (LEU) according to the conversion formula: 100 LEU = 100 mg regular levodopa, given with a peripheral decarboxylase inhibitor = 133 mg levodopa (plus peripheral decarboxylase inhibitor) in controlled-release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

The neurologist at the treatment centre completed an adverse-effects form 1 week after pallidotomy and at the time of the 6-month assessment.

The members of the data-monitoring committee were not involved in the study. An interim analysis by the data-monitoring committee was prospectively planned after the outcome assessments of the first 16 patients. The objective of the interim analysis was safety control. We sent a photocopy of every completed adverse-effects form to the committee.

Statistical analysis The sample-size estimation for the primary outcome was based on a two-sided two-sample *t* test with α=0.05, ß=0.20, and SD of 10 points in change scores in the two groups on the UPDRS motor section done in the off phase. A difference of 10 points in change scores between the pallidotomy group and the control group was considered a minimum important difference. We estimated that at least 17 patients would be needed in each treatment group.
All analyses were based on the intention-to-treat principle. Primary and secondary outcome factors at baseline and at follow-up after 6 months were described in median scores. The change scores of the pallidotomy and control patients were compared with the non-parametric Mann-Whitney *U* test. With regard to the patients' diaries, we analysed the difference between the mean symptom scores with unpaired *t* tests, and expressed these differences in 95 percent confidence interval (CI).

Figure Study profile



* Pallidotomy was not completed in one patient.

Results

During the study period, we enrolled and randomly allocated 37 patients (figure). The first patient included (pallidotomy group) refused follow-up assessment in the off phase, but all other outcome measures were obtained. During the study period, one patient (control group) died of a myocardial infarction. At the time of follow-up assessment, a second control patient could not be scored because of admission to an intensive-care unit for surgical complications after hip replacement (venous thrombosis, lung embolism, and pneumonia).

At baseline, the pallidotomy patients scored higher on the pain VAS and controls needed more frequently help with all activities of daily living (tables 2 and 6). The other baseline variables of the two groups were similar.

The median UPDRS motor off score in the pallidotomy group improved by 31 percent (from 47 to 32.5 points), whereas the median score for the control group worsened by 8 percent (52.5 to 56.5, table 3). The difference in change scores between pallidotomy and control patients was significant ($p<0.001$).

For off-phase assessment, the median pain VAS change scores did not differ significantly (table 3). For the disability scales, significant differences in change scores could be shown on the Barthel index ($p=0.004$), the UPDRS activities of

Table 2. Baseline of patient characteristics

	Pallidotomy group (n=19)	**Control group (n=18)**
Demographic variables:		
Sex (male/female)	8 / 11	9 / 9
Age (years)	60.6 (47-73)	64.2 (44-73)
Duration of disease (years)	15.0 (8-26)	17.5 (9-27)
Age at onset of PD (years)	45.0 (32-61)	47.0 (27-60)
Side of surgery (right/left)	13 / 6	
Medication (LEU)	925 (165-1600)	862.5 (175-1750)
Minimisation variables (number of patients):		
Centre 1	9	9
Centre 2	4	6
Centre 3	6	3
HY stage < 4 in off phase	8	7
HY stage 4 or 5 in off phase	11	11
Clinical rating scales:		
Hoehn and Yahr stage off/on	4 (3-5) / 2.5 (2-4)	4 (2-5) / 2.5 (1-4)
UPDRS motor off/on	47 (24-81) / 19 (1-49)	48.5 (23-82) / 18 (1-48)
Dyskinesia rating scale on	2 (0-3)	2 (0-3)
Pain VAS (mm) off/on*	27 (0-100) / 8 (0-53)	19.5 (0-87) / 4 (0-32)
Barthel Index off/on	11 (4-20) / 19 (14-20)	11.5 (3-19) / 20 (12-20)
UPDRS ADL off/on	30 (11-41) / 12 (4-24)	32 (14-45) / 11.5 (0-27)
Schwab and England scale off/on	40 (20-80) / 80 (50-90)	35 (10-80) / 80 (50-90)
PDQL on	113 (81-141)	106 (63-151)

Data are median (range) unless otherwise stated; * $p=0.02$ for the comparison between groups.

Table 3. Primary and secondary outcomes—median (range) scores of clinical rating scales for defined off phase assessment, n=18 for pallidotomy group and n=16 for control group

	Baseline	6 Months	Change	p*
Primary outcome				
UPDRS motor				
Pallidotomy group	47 (24-81)	32.5 (16-66)	15 (-13 to 27)	0.0004
Control group	52.5 (23-82)	56.5 (19-91)	-2 (-15 to 9)	
Secondary outcome				
Pain VAS (mm)				
Pallidotomy group	27 (2-100)	14 (0-69)	3.5 (-20 to 77)	0.13
Control group	15.5 (0-87)	22 (0-84)	-0.5 (-23 to 45)	
Barthel Index				
Pallidotomy group	10.5 (4-20)	18 (6-20)	2.5 (-2 to 11)	0.004
Control group	11.5 (3-19)	8 (4-19)	-0.5 (-7 to 3)	
UPDRS ADL				
Pallidotomy group	30 (11-41)	21 (8-38)	7 (-8 to 20)	0.002
Control group	32 (14-45)	35 (15-46)	-2 (-11 to 6)	
Schwab and England scale				
Pallidotomy group	35 (20-80)	70 (20-90)	15 (-10 to 40)	0.0009
Control group	35 (10-80)	30 (10-80)	-5 (-30 to 10)	

A positive change score signifies improvement; * Mann-Whitney *U* test.

Table 4. Secondary outcome—median (range) scores of clinical rating scales for defined on phase assessment, n=19 for pallidotomy group and n=16 for control group

	Baseline	6 Months	Change	p*
UPDRS motor				
Pallidotomy group	19 (1-49)	22 (5-54)	2 (-35 to 34)	0.24
Control group	18 (1-48)	22.5 (1-78)	-2 (-60 to 22)	
Dyskinesia rating scale				
Pallidotomy group	2 (0-3)	1 (0-2)	1 (-1 to 2)	0.02
Control group	2 (0-3)	2 (0-4)	0 (-1 to 3)	
Pain VAS (mm)				
Pallidotomy group	8 (0-53)†	4 (0-32)	3 (-24 to 51)	0.04
Control group	2.5 (0-30)	3.5 (0-26)	-0.5 (-11 to 11)	
Barthel Index				
Pallidotomy group	19 (14-20)	19 (12-20)	0 (-5 to 6)	0.99
Control group	20 (12-20)	20 (11-20)	0 (-6 to 2)	
UPDRS ADL				
Pallidotomy group	12 (4-24)	12 (4-26)	0 (-10 to 16)	0.09
Control group	10.5 (0-27)	12.5 (4-28)	-2.5 (-8 to 5)	
Schwab and England scale				
Pallidotomy group	80 (50-90)	80 (50-100)	0 (-20 to 40)	0.09
Control group	80 (50-90)	80 (30-90)	0 (-40 to 10)	
PDQL				
Pallidotomy group	113 (81-141)	88 (43-163)	19 (-44 to 57)	0.004
Control group	104 (61-141)	108 (61-141)	-2.5 (-18 to 23)	

A positive change score signifies improvement; * Mann-Whitney *U* test; † p=0.02 for the comparison between groups.

Table 5. Secondary outcome—median (range) scores of timed tests, expressed in seconds

	n*	Baseline	Change	p†
Off phase				
Tapping test contralateral				
Pallidotomy group	16	13.3 (7.0-30.6)	3.1 (-4.1 to 20.7)	0.04
Control group	16	11.9 (5.2-21.3)	-0.8 (-10.1 to 8.6)	
Tapping test ipsilateral				
Pallidotomy group	15	11.4 (6.0-25.8)	1.4 (-3.7 to 11.6)	0.18
Control group	16	11.7 (4.7-20.2)	0.3 (-6.4 to 7.7)	
Stand-walk-sit test				
Pallidotomy group	9	18.9 (9.9-42.8)	2.4 (0.9 to 28.2)	0.03
Control group	6	14.6 (8.5-22.7)	-0.3 (-12.3 to 8.1)	
On phase				
Tapping test contralateral				
Pallidotomy group	19	8.6 (4.7-26.2)	0.6 (-5.4 to 17.8)	0.46
Control group	16	8.1 (4.7-14.9)	-0.3 (-8.7 to 6.8)	
Tapping test ipsilateral				
Pallidotomy group	18	8.3 (4.3-20.9)	0.8 (-4.7 to 10.1)	0.21
Control group	16	7.8 (4.6-14.3)	-0.2 (-6.3 to 5.9)	
Stand-walk-sit test				
Pallidotomy group	14	13.0 (7.1-28.4)	1.1 (-3.7 to 16.1)	0.65
Control group	13	11.7 (7.6-39.5)	0.2 (-4.7 to 18.1)	

A positive change score signifies improvement; * number of patients who accomplished baseline and 6-month assessment timed tests; † Mann-Whitney *U* test.

daily living score (p=0.002), and the Schwab and England scale (p<0.001) in favour of the pallidotomy group (table 3). Not all the patients could accomplish all the timed tests. Compared to the control group, the contralateral tapping test (p=0.04) and the stand-walk-sit test (p=0.03) improved significantly in the pallidotomy patients (table 5).

For on-phase assessment, the median score on the dyskinesia rating scale improved one point in the pallidotomy group compared with no change in the control patients (p=0.02, table 4). The pallidotomy patients had a higher pain VAS score at baseline; at 6-month assessment the scores of both groups were similar (4 *vs* 3.5). The PDQL questionnaire made it clear that operated patients felt their lives had improved (p=0.004, table 4). With regard to the change scores on the other clinical scales and the timed tests (tables 4 and 5), no significant differences could be detected in the on phase.

The patients' symptom diaries showed that the time rated on without dyskinesias was significantly increased in the pallidotomy group by an average of 2.8 h per day (p=0.02, table 6). At the same time, pallidotomy patients rated less time on with dyskinesias and less time for parkinsonism. The latter changes were not significant.

The diaries describing functioning for activities of daily living showed that pallidotomy patients scored 1.0 h per day less help needed with some activities, while the control patients' score increased with 1.8 h (p=0.03, table 6). The

Table 6. Secondary outcome—patients' diaries (h per day), from 0600 h to 2400 h, mean (SD), n=18 for pallidotomy group and n=1 for control group

	Baseline	Change†	Difference in mean change scores (95% CI)	p*
Symptoms				
Sleep				
Pallidotomy group	2.9 (1.4)	0.3 (0.8)	0.2 (-0.4 to 0.8)	0.49
Control group	2.3 (1.3)	0.1 (0.9)		
Parkinsonism				
Pallidotomy group	6.6 (2.3)	-1.3 (2.9)	-1.4 (-3.3 to 0.6)	0.15
Control group	6.9 (2.3)	0.1 (2.5)		
On without dyskinesias				
Pallidotomy group	4.4 (3.0)	2.8 (3.2)	2.5 (0.4 to 4.6)	0.02
Control group	4.2 (2.8)	0.3 (2.6)		
On with dyskinesias				
Pallidotomy group	3.9 (3.0)	-1.8 (3.6)	-1.3 (-5.6 to 1.0)	0.26
Control group	4.6 (3.0)	-0.5 (2.7)		
Functioning				
Sleep				
Pallidotomy group	3.2 (1.6)	0.1 (0.9)	0.3 (-0.4 to 0.9)	0.40
Control group	3.0 (1.6)	-0.2 (0.9)		
Help needed with all ADL				
Pallidotomy group	2.3 (2.0)‡	-1.4 (1.6)	-0.2 (-1.7 to 1.3)	0.79
Control group	4.2 (2.1)	-1.2 (2.7)		
Help needed with some ADL				
Pallidotomy group	7.1 (2.8)	-1.0 (3.8)	-2.7 (-5.3 to -0.2)	0.03
Control group	5.3 (2.2)	1.8 (3.1)		
Independent				
Pallidotomy group	5.5 (3.9)	2.2 (4.1)	2.6 (0.0 to 5.3)	0.05
Control group	5.7 (3.1)	-0.4 (3.2)		

ADL=activities of daily living; * comparison of the change scores with the unpaired *t* test; † change score is 6-month assessment scores minus baseline scores; ‡ p=0.02 for the comparison between groups.

mean time pallidotomy patients were independent increased 2.2 h compared with a decrease of 0.4 h per day in the control group (p=0.05).

At assessment at 6 months, the medication in LEU was not changed. Pallidotomy patients used a median of 850 LEU (range 165 to 2075) and control patients 1000 LEU (range 400 to 2250). At baseline, one patient in the pallidotomy group had continuous subcutaneous apomorphine infusion, which was stopped after pallidotomy.

Nine of the 19 operated patients had adverse effects, two of whom had major adverse effects (table 7). One patient had dysarthria and a reduced consciousness for a few hours. At 6-month assessment he had dysphasia, drooling, and postural instability. In the second patient surgery had to be stopped due to psychosis after stopping the sedation with propofol. One lesion was made. The patient was admitted to a psychiatric hospital and remained intermittently psychotic. The patient had an episode of depression before participating in the trial. Seven

patients had mild adverse effects. In four of these patients adverse effects were still present at 6-month assessment (table 7).

Masking of the assessor was unsuccessful for four patients in the pallidotomy group (including one patient with severe adverse effects) and one control. Repeated analyses, without the data of these five patients, showed the same results.

Table 7. Secondary outcome—adverse effects

1 Week after surgery	6-Month assessment
Dysarthria, followed by reduced consciousness for few h, and pseudobuldar syndrome	Dysphasia, drooling and postural instability
Confused during surgery, surgery not completed	Intermittent hallucinations/psychosis
Reduced speech volume	Slight facial paresis, drooling, and fatigue
Hiccups	Loss of concentration
Urinary incontinence	Urinary incontinence
Facial paresis	Slight facial paresis and drooling
Urinary incontinence	None
Dysarthria, starting 3 days after surgery	None
Severe headache while supine starting 4 days after surgery, lasting a few days	None

Discussion

The results of our randomised trial support the findings of earlier cohort studies that unilateral pallidotomy reduces parkinsonism in the off phase by about 30 percent on the UPDRS motor scale. In addition, our trial confirmed a 50 percent reduction of levodopa-induced dyskinesias by unilateral pallidotomy. The cohort studies showed that the effects are most clear on the contralateral side of the body. Our findings are consistent with other reports on unilateral pallidotomy and alternative methods for target localisation such as magnetic resonance imaging, computed tomography, and microelectrode recording.[1,2,4,5,8,9] Because patients were aware of the treatment allocation, a part of the effect measured could be due to the placebo effect.

With regard to the other outcome measures, we found that unilateral pallidotomy improved patients' disability in the off phase, their perceived quality of life, and the contralateral tapping and stand-walk-sit test in the off phase.

Assessment in provoked off and on phases is becoming more and more standard in research on the effects of surgery for Parkinson's disease. However, interpretation of these results in the terms of daily life, in which patients may unpredictably fluctuate between episodes with predominantly parkinsonian symptoms and episodes with disabling dyskinesias, is difficult. Therefore, we feel the diaries may contribute to understanding of the impact of unilateral pallidotomy on daily life. The diaries showed that patients, after unilateral pallidotomy, were in the on phase without dyskinesias on average an extra 2.8

h. In addition, the time pallidotomy patients were independent increased on average by 2.2 h. Thus, besides improvement measured in standardised off and on phases, these results support the view that unilateral pallidotomy may lead to more independence in daily life.

Two of the 19 patients who underwent unilateral pallidotomy had major permanent adverse effects. In our study, three patients had only transient and four patients had permanent minor adverse effects. This proportion is in agreement with other reports, in which transient adverse effects vary between 5-60 percent and permanent effects in up to 40 percent. None of our patients had a symptomatic intracerebral haemorrhage or infarct. In previous studies on pallidotomy, these complications occurred in up to 20%.[1-4,8,9,23,24]

A remaining question is the place of pallidotomy in advanced Parkinson's disease in view of the results of cohort studies that investigated the effects of deep brain stimulation in the subthalamic nucleus.[25] The results of studies comparing both procedures have to be awaited.

Unilateral pallidotomy is therefore an effective treatment in patients with advanced Parkinson's disease, who respond unsatisfactorily to pharmacological treatment. Adverse effects, however, can be severe and this factor has to be considered when assessing patients for surgical treatment.

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