

PAPER

Effect of chronic pallidal deep brain stimulation on off period dystonia and sensory symptoms in advanced Parkinson's disease

T J Loher, J-M Burgunder, S Weber, R Sommerhalder, J K Krauss

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See end of article for authors' affiliations

Correspondence to:
Prof Dr J K Krauss,
Department of
Neurosurgery, University
Hospital, Klinikum
Mannheim,
Theodor-Kutzer-Ufer 1–3,
681 67 Mannheim,
Germany; joachim.krauss@
nch.ma.uni-heidelberg.de

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Objective: To investigate the efficacy of chronic pallidal deep brain stimulation (DBS) on off period dystonia, cramps, and sensory symptoms in advanced Parkinson's disease (PD).

Methods: 16 patients (6 women, 10 men; mean age at surgery 65 years) suffering from advanced PD were followed up prospectively for one year after implantation of a monopolar electrode in the postero-ventral lateral globus pallidus internus. Unilateral DBS was performed in 9 patients. 10 patients had bilateral procedures (contemporaneous bilateral surgery in 7 and staged bilateral surgery in 3 instances). The decision whether to perform unilateral or bilateral surgery depended on the clinical presentation of the patient. Patients were formally assessed preoperatively, at 3–5 days, 3 months, and 12 months after surgery.

Results: In patients who underwent unilateral surgery, pain was present in 7 (78%), off dystonia in 5 (56%), cramps in 6 (67%), and dysaesthesia in 4 (44%). In patients who underwent bilateral surgery, pain was present in 7 (70%), off dystonia in 6 (60%), cramps in 7 (70%), and dysaesthesia in 4 (40%). With unilateral DBS, contralateral off period dystonia was improved by 100% at 1 year postoperatively, pain by 74%, cramps by 88%, and dysaesthesia by 100%. There was less pronounced amelioration of ipsilateral off period dystonia and sensory symptoms. With bilateral DBS, total scores for dystonia were improved by 86%, for pain by 90%, for cramps by 90%, and for dysaesthesia by 88%. The benefit appeared early at the first evaluation 3–5 days after surgery and was stable throughout the follow up period.

Conclusions: Pallidal DBS yields major improvement of off period dystonia, cramps, and sensory symptoms in patients with advanced PD.

Functional stereotactic surgery is now well established for the treatment of the motor symptoms of advanced Parkinson's disease (PD). Chronic deep brain stimulation (DBS) nowadays is considered an accepted alternative to radio-frequency lesioning.^{1–4} Furthermore, chronic DBS has widened the spectrum of surgery for movement disorders, in particular with regard to bilateral procedures.^{5–6} The globus pallidus internus (GPi) and the subthalamic nucleus (STN) are the targets of choice for treatment of advanced PD in contemporary functional neurosurgery.^{7–10} It has been shown that chronic DBS of these targets yields a benefit both in motor function and in functional disability.

The effect of surgical treatment in patients with PD is assessed most commonly by the unified Parkinson's disease rating scale (UPDRS).¹¹ While the UPDRS allows appropriate evaluation of motor symptoms and functional disability, it is not suitable to determine changes in off period dystonia, cramps, and sensory symptoms, which are common features and a source of great discomfort in advanced PD. Shulman and colleagues recently reported a prevalence of sensory symptoms of 63% in patients with PD.¹² Thus far, however, data are scarce on the efficacy of stereotactic surgery with regard to off period dystonia, cramps, and sensory symptoms. No systematic study of the benefit of unilateral versus bilateral DBS has been published thus far.

Recently, we published the results of our one year follow up study on chronic pallidal DBS in 16 consecutive patients with advanced PD, showing major improvement in motor symptoms and functional disability.¹³ Here, we focus on the prospective assessment of the effect of pallidal DBS on off period dystonia, cramps, and sensory symptoms in advanced PD.

PATIENTS AND METHODS

Patients

Advanced idiopathic PD was diagnosed in all patients according to clinical criteria. All were responsive to levodopa but their parkinsonian symptoms were not sufficiently controlled. Furthermore, patients suffered from additional disability due to levodopa induced side effects, such as dyskinesias and on-off motor fluctuations. Exclusion criteria were major cognitive dysfunction, major depression or other psychiatric disorders, features suggestive of atypical parkinsonian syndromes, or abnormal brain scans such as major cerebral atrophy. Sixteen patients, 6 women and 10 men, were enrolled in the present study. Mean age at surgery was 64.9 years (range 49–77 years). Mean age at onset of parkinsonian symptoms was 46.9 years (range 32–59 years), and duration of symptoms before surgery was 18.2 years (range 6–30 years). Table 1 shows the baseline characteristics of the patients stratified according to whether they underwent unilateral or bilateral surgery.

Neurosurgical procedure

Unilateral procedures were performed in nine patients with a major lateralisation of symptoms. Three of them had secondary staged bilateral surgery later on. Seven patients who had higher scores for axial symptoms underwent primarily

Abbreviations: CT, computed tomography; DBS, deep brain stimulation; GPi, globus pallidus internus; PD, Parkinson's disease; STN, subthalamic nucleus; UPDRS, unified Parkinson's disease rating scale

Table 1 Baseline characteristics before surgery

Characteristic	Unilateral stimulation	Bilateral stimulation
Sex		
Male	6	5
Female	3	5
Age at operation (years)		
Mean (SD)	65.1 (5.4)	64.6 (9.9)
Range	57–71	49–77
Age at onset of disease (years)		
Mean (SD)	48.9 (7.4)	45.1 (8.1)
Range	34–57	32–59
Duration of disease (years)		
Mean (SD)	16.7 (6.3)	19.6 (7.9)
Range	10–27	6–30
Schwab and England activities of daily living score (%)		
Off period		
Mean (SD)	31.1 (15.4)	28.0 (15.5)
Range	20–60	10–60
On period		
Mean (SD)	56.7 (16.6)	51.0 (24.2)
Range	40–80	20–80
Hoehn and Yahr stage		
Off period		
Median	4.2 (0.8)	4.4 (0.7)
Range	3–5	3–5
On period		
Median	3.5 (0.5)	3.9 (0.9)
Range	3–4	3–5
Motor unified Parkinson's disease rating scale		
Off period		
Mean	57.2 (13.7)	63.4 (17.4)
Range	31–69	36–88
On period		
Mean	29.1 (6.5)	37.6 (17.3)
Range	19–39	15–59
Medication		
Levodopa/peripheral decarboxylase inhibitor (mean)	881.3	970.5
Total levodopa equivalent dose (mean)	1126.7	1235.5

The total levodopa equivalent dose was calculated as the sum of the dose of regular levodopa-carbidopa (or levodopa-benserazide), plus 0.75 times the dose of controlled release levodopa-carbidopa, plus 10 times the dose of bromocriptine, plus 100 times the dose of pergolide, plus 100 times the dose of pramipexole. For patients who were receiving tolcapone, the sum of the dose of regular levodopa and 0.75 times the dose of controlled release levodopa was multiplied by a factor of 1.33.

contemporaneous bilateral surgery. Monopolar DBS electrodes (3388, Medtronic Inc, Minneapolis, Minnesota, USA) were implanted into the posteroventral lateral GPi under computed tomographic (CT) stereotactic conditions, as reported in detail elsewhere.^{13–18} Microelectrode recording and macrostimulation techniques were used to further refine the target. The implantable pulse generators (Itrel II, Medtronic Inc) were placed in a subcutaneous pouch below the clavicle. Postoperatively, CT scans were done of all patients. The implantable pulse generator was first programmed within 24 hours after operation, in general, and stimulation settings were adjusted on follow up visits.

Clinical assessment and analysis of data

All patients underwent standardised assessments including UPDRS both off levodopa (practically defined off, 12 hours after overnight withdrawal of antiparkinsonian medication) and on levodopa (best on, after administration of levodopa), Hoehn and Yahr staging, Schwab and England activities of daily living scale, modified Obeso dyskinesia rating scale, mini-mental state examination, Hamilton depression scale, and a standardised video protocol. Additional information on dosage of levodopa and other antiparkinsonian drugs, patient diary for fluctuations, dyskinesia severity and location, and global clinical impression were obtained at each patient's visit. All formal evaluations were performed by the neurological team members.

In addition, the following off symptoms were evaluated: pain, dystonia, cramps, and dysaesthesia. The severity was

described by the patients according to an ordinal scale ranging from 0 to 4 (0=absent, 1=slight, 2=moderate, 3=pronounced, 4=severe). The rating for each off symptom was applied to six different parts of the body (neck, trunk, upper and lower extremities at each side) resulting in a maximal total score of 24 points. Follow up assessments were performed between 3–5 days postoperatively, at 3 months, and at 1 year after surgery.

Outcome measures at baseline and at defined follow up visits were described in mean scores separately for patients treated with unilateral and bilateral DBS. To investigate the hypothesis of a postoperative change we compared the follow up scores with the preoperative score using Wilcoxon's paired rank test (one tailed with regard to a supposed improvement). A *p* value of < 0.05 was considered to indicate significance.

RESULTS

Occurrence and severity of off period dystonia, cramps, and sensory symptoms

Table 2 shows the mean (SD) preoperative total scores of off period dystonia, cramps and sensory symptoms. After unilateral surgery, pain was present in seven of nine patients (78%), off dystonia in five (56%), cramps in six (67%), and dysaesthesia in four (44%). After bilateral surgery, pain was present in seven of 10 patients (70%), off dystonia in six (60%), cramps in seven (70%), and dysaesthesia in four (40%). Off period dystonia most frequently affected the toes or feet, while cramps usually affected the thighs. Typically, cramps could be relieved by massaging the thighs.

Table 2 Occurrence and severity of off period dystonia, cramps, and sensory symptoms

Off symptom	Unilateral stimulation	Bilateral stimulation
Pain		
Number of patients	7	7
Mean (SD) total score	9.0 (5.3)	8.0 (5.9)
Dystonia		
Number of patients	5	6
Mean (SD) total score	3.4 (2.3)	3.5 (2.6)
Cramps		
Number of patients	6	7
Mean (SD) total score	3.5 (3.4)	6.0 (5.7)
Dysaesthesia		
Number of patients	4	4
Mean (SD) total score	4.5 (3.5)	6.0 (7.4)

Operative morbidity and follow up

There were no intraoperative complications. Postoperatively, one patient had a haemorrhage at the site of the pacemaker, which required revision. Another patient had a small asymptomatic pallidal haematoma, which was detected on routine postoperative CT and had a prolonged micropallidotomy effect. All patients were available for follow up. One patient who had bilateral surgery died seven months after surgery secondary to urosepsis. The one year follow up was obtained 18 months after surgery in one patient. In the three patients who underwent contralateral surgery later on, the last available follow up at nine months was used. Thus, the mean follow up was 11.7 months. All patients had continuous stimulation. The mean values of settings at the one year follow up were as follows: amplitude 1.4 V (range 0.8–2.0), frequency 146 pulses/s (range 125–160), and pulse width 210 µs in patients with unilateral stimulation; and amplitude 1.0 V (range 0.6–1.8), frequency 138 pulses/s (range 130–145), and pulse width 210 µs in patients with bilateral stimulation.

Clinical outcome

Detailed data regarding the cardinal symptoms of PD according to off period and on period UPDRS assessments have been published previously.¹³ In summary, in patients with unilateral GPi DBS the UPDRS activities of daily living score off levodopa improved by 34% at three months and by 33% at 12 months, while the motor off score decreased by 38% at three months and by 38% at 12 months. Bilateral DBS ameliorated the activities of daily living off score by 36% at three months and by 34% at 12 months, while there was a 36% improvement of the motor off score at three months and a 41% improvement at 12 months. There was also significant improvement of on

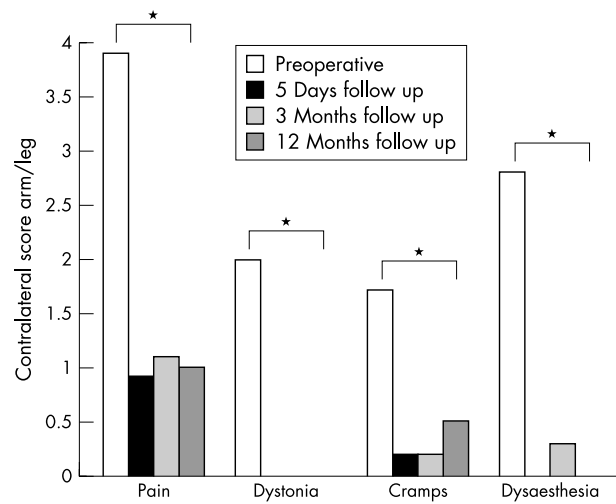


Figure 1 Effect of unilateral deep brain stimulation of the globus pallidus internus on off period dystonia, cramps, and sensory symptoms. Mean baseline scores and follow up scores (percentage improvement compared with preoperative scores) during continuous pallidal stimulation are shown. Bar graphs display the unilateral scores of the arm and leg contralateral to the stimulation site.

symptoms and of on-off fluctuations. There were no significant changes in levodopa medication or levodopa equivalents.

Postoperative assessment of off period dystonia, cramps, and sensory symptoms

Dystonia, cramps, and sensory symptoms did not develop in the follow up period, if not already present at the preoperative assessment. In patients undergoing unilateral GPi DBS there was a significant and sustained improvement of contralateral off period dystonia (–100%, $p = 0.019$), pain (–74.4%, $p = 0.009$), cramps (–88.2%, $p = 0.020$), and dysaesthesia (–100%, $p = 0.033$) throughout the follow up period up to one year (table 3). The benefit appeared early at the first postoperative evaluation within days after surgery (fig 1). There were no significant differences between the ratings of the 3 month and the 12 month evaluation (table 3). Ipsilateral off period dystonia, pain, cramps, and dysaesthesia had also improved at the one year follow up; however, the improvements were less pronounced and not significant. No useful statistical analysis of the effect of unilateral GPi DBS on ipsilateral off period dystonia and sensory symptoms could be done in the three patients who underwent staged bilateral surgery. Two of the three patients who first had unilateral stimulation and underwent contralateral stimulation later on had only marginal scores for ipsilateral off period dystonia and

Table 3 Off period dystonia, cramps, and sensory symptoms before, 3–5 days after, 3 months after, and 12 months after unilateral deep brain stimulation of the globus pallidus internus

Off period symptom	Score range	Follow up									
		Baseline	5 Days	Change 0–5 days (%)	p Value	3 Months	Change 0–3 months (%)	p Value	12 Months	Change 0–12 months (%)	p Value
Dystonia total score	0–24	3.4 (2.3)	0.2 (0.4)	–94.1	0.021	0.4 (0.9)	–88.2	0.021	0.4 (0.9)	–88.2	0.021
Dystonia contralateral score	0–8	2.0 (0.7)	0.0 (0.0)	–100	0.019	0.0 (0.0)	–100	0.019	0.0 (0.0)	–100	0.019
Pain total score	0–24	9.0 (5.3)	2.4 (5.2)	–73.3	0.009	2.9 (4.3)	–67.8	0.009	2.6 (2.8)	–71.1	0.009
Pain contralateral score	0–8	3.9 (2.0)	0.9 (2.3)	–76.9	0.014	1.1 (2.3)	–71.8	0.014	1.0 (1.5)	–74.4	0.009
Cramps total score	0–24	3.5 (3.4)	0.5 (0.8)	–85.7	0.013	0.2 (0.4)	–94.3	0.013	0.7 (0.8)	–80.0	0.021
Cramps contralateral score	0–8	1.7 (1.4)	0.2 (0.4)	–88.2	0.020	0.2 (0.4)	–88.2	0.020	0.5 (0.8)	–88.2	0.020
Dysaesthesia total score	0–24	4.5 (3.5)	0.0 (0.0)	–100	0.034	0.3 (0.5)	–93.3	0.033	0.0 (0.0)	–100	0.034
Dysaesthesia contralateral score	0–8	2.8 (2.1)	0.0 (0.0)	–100	0.033	0.3 (0.5)	–89.3	0.055	0.0 (0.0)	–100	0.033

Mean baseline scores and follow up scores (percentage improvement compared with preoperative score) during continuous pallidal stimulation are shown.

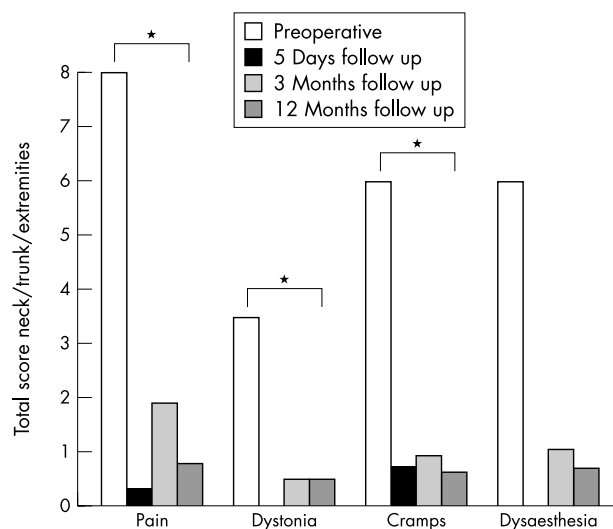


Figure 2 Effect of bilateral deep brain stimulation of the globus pallidus internus on off period dystonia, cramps, and sensory symptoms. Mean baseline scores and follow up scores (percentage improvement compared with preoperative scores) during continuous pallidal stimulation are shown. Bar graphs display the totals scores of neck, trunk, and both upper and lower extremities.

sensory symptoms. The total scores in patients with unilateral stimulation, including the ratings for the neck and trunk, also reflected major improvement of off dystonia (−88.2%, $p = 0.021$), pain (−71.1%, $p = 0.009$), cramps (−80.0%, $p = 0.021$), and dysaesthesia (−100%, $p = 0.034$).

In patients with bilateral stimulation the total score for dystonia improved by 85.7% ($p = 0.021$), for pain by 90.0% ($p = 0.014$), for cramps by 90.0% ($p = 0.021$), and for dysaesthesia by 88.3% ($p = 0.090$) at the one year follow up (fig 2). Again, the improvements were sustained throughout the follow up period. As with unilateral stimulation, there was no significant change between the 3 month and the 12 month follow up assessments.

DISCUSSION

Our study clearly shows that chronic pallidal stimulation ameliorates off period dystonia, cramps, and sensory symptoms in advanced PD. In patients undergoing unilateral surgery there was a distinct and significant contralateral stimulation effect, whereas the improvement of ipsilateral symptoms was less striking. In the bilateral stimulation group there was also major improvement of all corresponding total scores for pain, dystonia, cramps, and dysaesthesia. The benefit appeared early and remained stable throughout the follow up at one year.

The frequency of off period dystonia and sensory symptoms in our patients is similar to that seen in other series of patients with advanced PD.^{19–24} Pain was the most frequently reported symptom, present in more than 70% of patients. Quinn and colleagues have shown a strong association between off period dystonia and pain, which is in accordance with the findings in our study.²⁰ Off period dystonia and pain can be rather vexing and disabling features of advanced PD. Pain and dystonia off medication are found more frequently in patients with young onset PD.²⁵ Cramps appear to occur more often off levodopa in advanced PD.

Only a few studies have addressed the impact of functional stereotactic surgery on off period dystonia and pain in patients with advanced PD. In a prospective one year follow up study of 21 patients with PD undergoing unilateral pallidotomy, Honey and colleagues found a sustained significant reduction of pain of about 40%.²⁶ This result is consistent with findings of the

effectiveness of pallidotomy in two other studies that reported major reduction of “pain and discomfort scores” in 9 of 12 patients²⁷ and a very good effect with abolition of dystonia and pain in 12 of 24 patients.²⁸ Only one study reported on the effectiveness of GPi DBS for off period dystonia with complete relief in four patients and a major reduction in one of nine patients.²⁹ In two other studies, the Grenoble group described striking effects of bilateral STN DBS on off period dystonia and pain. In their 12 month follow up study of 16 patients with painful off period dystonia, they reported complete relief of dystonia and pain in 12 patients and a decrease in the other 4 patients.³⁰ In another study of eight patients with severe off period dystonia major improvement of dystonia (−90%) and pain (−66%) was found at the six month follow up assessment.³¹

According to the current model of basal ganglia pathophysiology in PD, it is thought that the cardinal symptoms of PD are secondary to increased neuronal activity of the STN and GPi subsequent to striatal dopamine depletion.^{32–34} The mechanisms underlying off period dystonia are not completely understood but it has been proposed that it may also be related to neuronal hyperactivity. Ablative surgery and DBS of the STN or of the GPi therefore has a rational basis and has been shown to be effective for both targets in clinical practice. The improvement in off motor function appears to be higher in STN DBS than in GPi DBS. While STN DBS and GPi DBS have different profiles regarding the alleviation of on period dyskinesias early after surgery, the alleviation of off period dystonia appears to be comparable. The similar effect on off period dystonia may be related to common functional mechanisms.^{31 35 36}

Apart from dystonia and pain, the presence of off period dysaesthesia in advanced PD is puzzling. The sensory function of the basal ganglia is not well known.^{37–39} It is thought that the basal ganglia control automatic or highly trained movements in relation to sensory input. The basal ganglia circuitry has also been postulated to “gate” sensory processing. Several studies found somatosensory deficits and abnormalities of sensorimotor integration and proprioception in patients with PD.^{12 40–46} Studies of somatosensory evoked potentials in PD patients have given conflicting results. While some groups showed decreased parietal N20 and frontal N30 somatosensory evoked potentials components in patients with PD,^{47–49} others failed to replicate these findings.^{50–52} In a recent positron emission tomography study, a distinct reduction of sensory evoked brain activation was found in contralateral cortical (parietal and frontal) and subcortical (globus pallidus and putamen) structures in patients with PD.⁵³

In conclusion, the present study shows that patients with PD with off period dystonia, cramps, and sensory symptoms benefit greatly from pallidal DBS. Disabling off period dystonia in advanced PD alone may be considered to be a good indication for functional stereotactic surgery. Further comparative studies are needed to decide which target is best suited in the individual patient. Long term results are still limited and it will be important to investigate the chronic effects of prolonged stimulation.

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Authors' affiliations

TJ Loher, JM Burgunder, S Weber, R Sommerhalder, Department of Neurology, Inselspital, University of Berne, Berne, Switzerland
J K Krauss, Department of Neurosurgery, University Hospital, Klinikum Mannheim, Mannheim, Germany

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