

Deep brain stimulation of the subthalamic nucleus: effectiveness in advanced Parkinson's disease patients previously reliant on apomorphine

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Objectives: To assess the efficacy of bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) in patients with advanced Parkinson's disease previously reliant on apomorphine as their main antiparkinsonian medication.

Methods: Seven patients with motor fluctuations despite optimal medical treatment given as predominantly apomorphine infusion (n=6), or intermittent apomorphine injections (n=1) underwent bilateral STN DBS using frameless stereotactic surgery. Standard assessments of parkinsonism and motor fluctuations, using Unified Parkinson's Disease Rating Scale (UPDRS) were performed before and six months after surgery. Assessments were performed both on and off medication, and postoperative with the stimulators switched on and off.

Results: Bilateral STN DBS improved motor scores (UPDRS III) by 61% when off medication (p<0.05). Clinical fluctuations (UPDRS IV items 36–39) were reduced by 46.2% (p<0.05). Total daily apomorphine dose was reduced by 68.9% (p<0.05) and apomorphine infusion via a pump was no longer required in four patients. There were no operative complications. Two patients required treatment for hallucinations postoperatively but there was no significant change in mini-mental state examination.

Conclusions: In patients with advanced Parkinson's disease, previously reliant on apomorphine, bilateral STN DBS is an effective treatment to reduce motor fluctuations and enable a reduction in apomorphine use.

Long term treatment of Parkinson's disease with levodopa may result in the emergence of motor fluctuations and dyskinesia.¹ There are a number of strategies used to minimise these complications including the use of directly acting dopamine receptor agonists. In patients with advanced disease in whom oral medication is ineffective or intolerable, intermittent subcutaneous injection of the dopamine receptor agonist, apomorphine can be very effective.² Longer term infusion of apomorphine over several hours a day is often required in patients with marked motor fluctuations.^{2–4} The use of apomorphine by infusion, and thus the management of such advanced patients, varies between movement disorder centres. Because of availability in the UK, there is a higher use of apomorphine infusion compared with centres in North America. Within the UK, our centre, has one of the highest uses of apomorphine.

The main alternative for such advanced patients in centres where apomorphine infusion is not widely adopted is surgical treatment. Currently bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a recognised treatment option for such patients with advanced Parkinson's disease. In general, studies published from movement disorders centres in America and Europe have shown the benefits of STN DBS in younger patients in whom levodopa and oral dopamine receptor agonists are the main stay of treatment.^{5–9} The series reported by Limousin *et al*⁵ included 10 patients who were using apomorphine before surgery, however, it is not clear if these patients were using intermittent subcutaneous injections or infusion.

To date, there are no case series published reporting the efficacy of bilateral STN DBS in patients with advanced Parkinson's disease all previously requiring apomorphine infusion as the main antiparkinsonian medication. In view of our extensive experience of apomorphine treatment of

advanced Parkinson's disease in our centre, we evaluated our experience of bilateral STN DBS in such patients. We present the results of six months follow up on seven patients in whom subcutaneous apomorphine was the principal preoperative antiparkinsonian drug.

METHODS

Patients

Seven patients (all male), mean (SD) age 61.0 (8.1) years, with advanced Parkinson's disease (according to UK Brain Bank criteria¹⁰), Hoehn and Yahr rating off medication 4–5, and on medication 2.5–4, mean (SD) disease duration 11.6 (4.6) years, were selected for bilateral STN surgery. Patients with a history of cognitive or psychiatric problems were excluded. All patients were levodopa responsive but despite optimal medication were experiencing motor fluctuations and dyskinesia. On average the proportion of the day when the patients were switched "off" was 26%–50% and when switched "on", dyskinesia was present for an average 26%–50% of the day. Median total UPDRS off medication was 120 (range 109–157) and on treatment was 66 (range 53–94).

All patients were using apomorphine as the principal antiparkinsonian medication. Six of the seven patients were receiving apomorphine via subcutaneous infusion (mean (SD) total daily dose 75.7 (45.9) mg) over mean 12 hours (range 10–12 h)/day (table 1). Four of these patients also used additional subcutaneous intermittent injections. One of the

Abbreviations: STN, subthalamic nucleus; DBS, deep brain stimulation; UPDRS, Unified Parkinson's Disease Rating Scale; ADL, activities of daily living; MMSE, mini-mental state examination

Table 1 Individual ant-parkinsonian medication before and six months after bilateral STN DBS implantation

Patient	Preoperative			Postoperative			Percentage change in daily levodopa equivalent	Percentage change in total daily apomorphine
	Levodopa equivalent (mg/d)	Apo infusion (mg/d)	Apo sc (mg/d)	Levodopa equivalent (mg/d)	Apo infusion (mg/d)	Apo sc (mg/d)		
1	3600	150	60	800	100	42	-60.5	-32.4
2	2350	75	15	980	0	15	-58.3	-83.3
3	1505	30	3	1105	0	9	-26.6	-72.3
4	2775	120	0	1200	0	0	-56.8	-100
5	540	45	9	780	45	12	+44.4	+5.6
6	1100	30	0	400	0	0	-63.6	-100
7	2600	0	80	1500	0	0	-42.3	-100

Apo, apomorphine; sc, subcutaneous. Percentage change is between preoperative and postoperative dose. Levodopa equivalent dose is defined in the text.

seven patients was using apomorphine as intermittent subcutaneous only (total daily dose 60–80 mg). No patients were experiencing side effects with apomorphine use. Six patients were also using levodopa and oral dopamine receptor agonists (table 1). The mean (SD) total daily levodopa “equivalent” dose of 2067 (1064) mg/d was adapted from Lozano *et al*,¹¹ (100 mg levodopa = 10 mg apomorphine = 1 mg pergolide = 3 mg ropinirole). One patient had a left pallidotomy, three years previously. All patients gave written informed consent.

Surgery

Surgery was performed using a neurosurgical robot (ISS NeuroMate). The robot has been shown to have accuracy in clinical use comparable to that of stereotactic frames, mean error <3 mm.¹² The robot is used in a frameless mode, requiring the implantation of skull based fiducials before imaging. Magnetic resonance imaging (MRI) was performed under general anaesthetic on the day before surgery. Axial T2 slices were acquired, with multiple acquisitions to improve image quality. Total scan time for this protocol was about 50 minutes. Images were then transferred to a planning station and reformatted. The STN was directly identified from the images, a trajectory planned to the target from a frontal burr hole, avoiding the ventricles and eloquent structures.

Surgery was performed under local anaesthetic with the patient off medication. To identify the functional target, microelectrode recordings were performed using FHC tungsten microelectrodes. Macroelectrode stimulation (pulse width 60 μ s, frequency 135 Hz) was performed once the STN had been identified. Accuracy of the target was assessed by improvement in arm and leg rigidity, bradykinesia (finger taps) and tremor, without inducing side effects. A deep brain electrode was then implanted and externalised for temporary external stimulation. All patients were implanted bilaterally during the same operating period. Five days later a dual channel pulse generator (Kinetra, Medtronic) was implanted into the infraclavicular fossa under general anaesthetic.

Postoperative adjustment to electrical parameters of pulse width, frequency and voltage, electrode contact, and polarity (mono or bipolar) were performed using a console programmer until optimal antiparkinsonian effects were seen, without side effects (table 2). A concomitant change in medication was made according to the effects of stimulation. Adjustments were made as often as required by the patient until a stable effect was achieved both off and on medication.

Clinical evaluations

All patients were assessed preoperatively, within one month of surgery. Parkinsonian motor scores were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS part III).¹³ The same observer performed all assessments. Unblinded evaluations were made “off medication” after an overnight

withdrawal of all antiparkinsonian medication and “on medication” when the best improvement in motor function after the patient's normal morning dose of antiparkinsonian medication was seen. Activities of daily living (ADL) were assessed using UPDRS part II. Clinical fluctuations and dyskinesia were assessed using UPDRS part IV. Dyskinesia severity was assessed, blind to treatment, by post hoc video analysis using a dyskinesia scale based on rating different body parts.¹⁴ A mini-mental state examination (MMSE) was also performed.

Assessments were repeated at six months after surgery, with stimulation switched on at optimal parameters, in both off and on medication, and after switching off the stimulator for at least 30 minutes, off and on medication. For on medication assessments, the patients received the same dose of morning medication as had been used preoperatively. Patient 1 was assessed at eight months after surgery.

Statistical analysis

The preoperative and postoperative non-parametric scores for UPDRS motor part III, dyskinesia severity and UPDRS part II ADL were compared using analysis of variance Friedman test and post hoc Dunn's multiple comparison test for variables of surgery (before and after surgery), stimulation (on and off stimulator), and medication (on and off medication) or by the paired Wilcoxon signed rank test. Preoperative and postoperative UPDRS part III subscores for tremor, rigidity, bradykinesia, gait and postural stability, on and off medication, were compared using Wilcoxon signed rank test. UPDRS part IV and MMSE preoperative and postoperative scores were compared using Wilcoxon signed rank test. Antiparkinsonian medication preoperatively and postoperatively was compared using a paired *t* test. Significance in all cases was assigned when $p < 0.05$.

RESULTS

Motor scores

There was a significant improvement in UPDRS part III motor scores at six months postoperatively compared with preoperatively ($p < 0.0001$) (fig 1). Thus preoperative UPDRS part III off medication improved by 61% postoperatively when on stimulation and off medication ($p < 0.05$) and by 71% on stimulation, on medication ($p < 0.001$) (fig 1). There was no significant improvement postoperatively either on or off medication when the stimulator was switched off, compared with preoperative on or off medication ($p > 0.05$, for all conditions). Off medication subscores of the UPDRS part III for tremor, rigidity, bradykinesia, gait, and postural stability were all significantly improved postoperatively, with stimulation on when compared with preoperatively off medication ($p < 0.05$ for all scores, table 3). When compared in the on medication

Table 2 Individual patient stimulator settings at six months after bilateral STN DBS implantation

Patient	Amplitude (v)		Electrode contact		Pulse width (μ s)	Frequency (Hz)
	Left STN	Right STN	Left STN	Right STN		
1	2.4	2.4	3-,C+ (M)	7-,C+ (M)	90	160
2	2	2	2-,C+ (M)	5-,C+ (M)	90	140
3	3.6	3.6	1-,3+ (B)	5-,6+ (B)	90	150
4	3.6	4	2-,C+ (M)	7-,C+ (M)	90	145
5	3.6	3.4	1-,C+ (M)	5-,C+ (M)	90	130
6	2.5	3.4	3-,C+ (M)	4+,5- (B)	90	145
7	2.6	2.8	1-,C+ (M)	5-,C+ (M)	90	145

STN, subthalamic nucleus; C, case; B, bipolar; M, monopolar.

Table 3 Effect of bilateral STN DBS on UPDRS part II activities of daily living (ADL) and part III subscores, both on and off medication. Postoperative scores are all with stimulation on. Data show median (and range), maximum possible scores are also shown. Percentage change is between preoperative and postoperative condition

UPDRS subscale	On medication				Off medication			
	Preoperative	Postoperative stimulator on	Significance	Percentage change	Preoperative	Postoperative stimulator on	Significance	Percentage change
ADL (0–52)	15 (3–33)	14 (4–25)	p<0.05	18.7%	38 (14–43)	25 (8–33)	p<0.05	30.6%
Tremor (0–28)	2 (0–20)	0 (0–8)	NS	37.1%	12 (2–26)	2 (0–11)	p<0.05	67%
Rigidity (0–20)	5 (0–15)	1 (0–10)	p<0.05	72.1%	12 (9–15)	4 (0–11)	p<0.05	65%
Bradykinesia (0–32)	17 (6–29)	13 (6–22)	NS	10.9%	28 (21–32)	16 (12–31)	p<0.05	36%
Gait (0–4)	2 (0–3)	1 (0–3)	NS	23.8%	3 (1–4)	1 (1–3)	p<0.05	50%
Postural stability (0–4)	2 (0–3)	1 (0–2)	NS	33.3%	4 (2–4)	1 (1–2)	p<0.05	61%

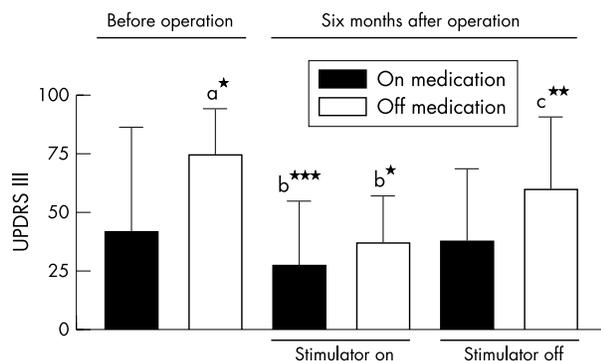


Figure 1 Graph showing median (and range) Unified Parkinson's Disease Rating Scale UPDRS part III motor scores preoperative and six months postoperative after bilateral STN DBS, both on and off medication and with stimulation on and off. Maximum possible UPDRS III score is 108. *p<0.05, *** p<0.001, n = 7. a=compared with preoperative on medication; b=compared with preoperative off medication; c=compared with postoperative on medication, stimulator on.

state, preoperatively and postoperatively, only rigidity subscores was significantly improved (table 3). There was no significant change in UPDRS part III subscores with the stimulator switched off, both on and off medication compared with preoperatively (p>0.05 for all conditions, data not shown).

Activity of daily living

UPDRS part II ADL scores, on and off medication, were significantly improved by surgery (p<0.001). ADL scores were improved by 60.9% postoperatively, stimulation on, on medication compared with preoperatively off medication (p<0.01). When compared with respect to medication, postoperative ADL score off medication significantly improved by 30.6% compared with preoperative off medication (p<0.05)

and postoperative on medication improved by 18.7% compared with preoperative on medication (p<0.05) (table 3).

Fluctuations and dyskinesia

There was a significant reduction in motor fluctuations, including the proportion of the day spent "off", "wearing off", and "sudden, unpredictable offs" after surgery. Thus preoperative clinical fluctuations were reduced by 46.2% postoperatively (UPDRS part IV, items 36–39, median 5 (range 2–6) and median 2 (range 1–3), p<0.05). The proportion of the day spent "off" was reduced from median 26%–50% of the day preoperatively to median 0% postoperatively (UPDRS part IV item 39 median 2 (range 1–3) and median 0 (range 0–1) respectively, p<0.05).

Dyskinesia duration and severity was also significantly reduced by 44% compared with preoperatively (UPDRS part IV, items 32, 33, 34 median 2 (range 1–5) and 6 (range 3–10) respectively, p<0.05). The proportion of the day with dyskinesia was significantly reduced by bilateral STN stimulation. Thus preoperatively, dyskinesia was present for median 26%–50% of the day compared with median 1%–25% of the day postoperatively (UPDRS part IV, item 32 median 2 (range 1–3) and median 1 (range 1–2) respectively, p<0.05).

Bilateral STN DBS significantly improved dyskinesia severity scores as assessed by post hoc video analysis (p<0.0001). Postoperatively with the stimulator on, off medication, dyskinesia was reduced by 85.9% compared with preoperatively on medication (median dyskinesia 0 (range 0–3) compared with 5 (range 3–20) respectively, p<0.05). There was a non-significant reduction in dyskinesia by 48% when compared preoperatively and postoperatively, on medication. When the stimulator was switched off postoperatively and on medication, dyskinesia was significantly reduced by 75.9% compared with preoperatively on medication (median dyskinesia 0 (range 0–11) compared with 5 (range 3–20), respectively, p<0.05).

Medication

Daily total levodopa equivalent medication was significantly reduced by 37.1% from 2067.1 (1064.4) mg/d to 1055 (379.7) mg/d ($p < 0.05$) (table 1). The apomorphine total daily dose was significantly reduced by 68.9% from 88.1 (62.6) mg/d to 31.9 (52.6) mg/d ($p < 0.05$). Four patients no longer required an apomorphine pump postoperatively, two of these patients remained on small doses of apomorphine by intermittent subcutaneous injection (patients 2 and 3). Two patients still required apomorphine pumps postoperatively. In patient 1 the dose was reduced from 150 mg to 100 mg, while patient 5 had been on apomorphine alone preoperatively and remained on 45 mg postoperatively with additional oral levodopa (table 1).

Side effects

Bilateral STN DBS had no significant effect on MMSE ($p > 0.05$). Thus median preoperative MMSE was 29 (range 29–30) compared with 29 (25–30) postoperative. One patient required early revision of connection wires because of wire fracture within two weeks of surgery. Most patients experienced transient parasthesias after switching on the stimulator. One patient developed disinhibited behaviour, which responded to a reduction in levodopa. Two patients required treatment with quetiapine for visual hallucinations, which developed several weeks after surgery.

DISCUSSION

This case series confirms the findings of previous reports that bilateral STN DBS is an effective treatment for patients with advanced Parkinson's disease.^{5–9} Significant improvements were seen in all parkinsonian symptoms. In patients previously reliant on apomorphine infusion, this surgical intervention enabled four of six patients either to disperse with apomorphine or to switch from an infusion to a lower dose given as intermittent subcutaneous injections. This has resulted in a great improvement in the patient's and carer's quality of life. Longer follow up of these patients is required to determine if this initial improvement at six months is maintained.

The practice at our centre of using apomorphine infusion as a treatment for motor fluctuations is such that the patients presented here were at a more advanced stage compared with other previously reported groups. Thus the mean (SD) UPDRS part III (motor score) preoperatively off medication was in general higher in our series at 74.3 (10.1) compared with other case series (where figures are available) for example, 59.0 (10.1),⁵ 55.7 (12.1),⁶ 67.6 (9.9),⁷ 49.6 (14),⁸ 54 (15.1).¹⁵ Despite this, the overall reduction in motor scores UPDRS part III (preoperative off medication compared with postoperative off medication, stimulation on) at 61% is comparable with other groups where UPDRS part III improved by between 42%–71% after six months.^{5–9, 15} Despite the severity of Parkinson's disease in these patients, there was little difference in age at surgery or disease duration compared with other groups. This suggests that bilateral STN DBS is equally effective in these very advanced patients.

In keeping with other studies, there was an overall reduction in medication postoperatively. Of importance in this series, is that four of six patients no longer required apomorphine infusion via a pump and the patient previously reliant on intermittent subcutaneous injections no longer required apomorphine. The two patients still requiring apomorphine via an infusion pump were at a more advanced stage (UPDRS part III off medication scores 94 and 78) and had continued disability despite optimal stimulation. However, improvements in other aspects of daily life were seen that both patients and carers found of benefit; in particular, improved sleep patterns, reduction in drooling saliva, and some improvement in off period pain.⁵ Limousin *et al*, similarly reported a marked reduction in apomorphine use after

surgery, such that only 1 of 10 patients were still requiring apomorphine at low dose (6 mg/d).

Bilateral STN DBS also resulted in a significant reduction in off period motor fluctuations by 46.2%. The commonest indication for apomorphine use in this series of patients was for off period complications but with variable benefit. Off period pain also responded well to surgery. Two patients required morphine preoperatively that was stopped postoperatively. Thus, in patients where off periods are an important source of disability, bilateral STN DBS seems to be more effective than apomorphine infusion.

In keeping with previous reports,^{5–9, 15} dyskinesia was also reduced after surgery; both assessed from historical data (UPDRS part IV) and by blinded post hoc video analysis. Of interest, there was a reduction in dyskinesia compared with preoperatively when the stimulator was switched off and after administration of the same preoperative morning antiparkinsonian medication. This would suggest that long term stimulation may “deprime” the patient such that the same dose of levodopa has an equivalent antiparkinsonian action (that is, there was no significant change in UPDRS part III between preoperative on medication and postoperative on medication, stimulation switched off) but there is less dyskinesia after bilateral STN DBS. This finding has been previously noted and discussed by other centres.^{16, 17} Dyskinesia reduction after bilateral STN DBS is thought to be primarily attributable to a concomitant reduction in medication. However, there is probably an effect on basal ganglia circuitry in addition whereby continuous STN DBS changes neural pathways responsible for the generation of levodopa induced dyskinesia.

No formal cognitive testing was performed in this series but median MMSE score was unchanged. Two patients developed hallucinations postoperatively that did not respond to reduction of antiparkinsonian medication and required additional treatment with the atypical anti psychotic agent, quetiapine. Despite the advanced stage of Parkinson's disease in our cohort of patients, no other cognitive problems were encountered. However, in view of accumulating evidence that cognitive problems may occur particularly in patients over 70 years,¹⁸ practice in our centre has now changed to include a full neuropsychological evaluation before surgery.

The neural mechanisms underlying Parkinson's disease involve overactivity of the STN.^{19–21} Levodopa and dopamine receptor agonists, including apomorphine, reduce overactivity of the STN and thus alleviate parkinsonian symptoms.^{22, 23} Bilateral STN DBS is thought to also reduce STN overactivity, although the exact mechanism of action is as yet unknown.^{24, 25} Thus both medical and surgical treatment, by reducing overactivity of the STN, will alleviate parkinsonism. Continuous daily apomorphine infusion would be thought to have similar antiparkinsonian effects to continuous bilateral STN DBS. A study measuring cortical inhibition following a single dose of apomorphine and STN stimulation has shown comparable effects.²⁶ Our study would suggest that bilateral STN DBS may be superior to apomorphine infusion, but this may simply relate to the continuous 24 hour DBS as compared with between 10 to 12 hours apomorphine. However, to date, the antiparkinsonian effects of apomorphine infusion and bilateral STN DBS surgery have not been compared in a randomised clinical trial. A multicentre study is currently underway in the UK (PD-SURG) in which Parkinson's disease patients in whom there is uncertainty as to whether surgical treatment is the next option are randomised to surgery (bilateral STN DBS) or best medical treatment and deferred surgery for 12 months. Patients randomised to the medical treatment arm may receive apomorphine infusion. This study may therefore permit such a comparison of bilateral STN DBS and apomorphine infusion including the cost effectiveness of such treatment options.

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