PAPER

Clinical and neuropsychological follow up at 12 months in patients with complicated Parkinson's disease treated with subcutaneous apomorphine infusion or deep brain stimulation of the subthalamic nucleus

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Background: The clinical condition of advanced Parkinson's disease (PD) patients is often complicated by motor fluctuations and dyskinesias which are difficult to control with available oral medications.
Objective: To compare clinical and neuropsychological 12 month outcome following subcutaneous apomorphine infusion (APO) and chronic deep brain stimulation of the subthalamic nucleus (STN-DBS) in advanced PD patients.
Methods: Patients with advanced PD and medically untreatable fluctuations underwent either APO (13 patients) or STN-DBS (12 patients). All patients were clinically (UPDRS-III, AIMS, 12 h on-off daily) and neuropsychologically (MMSE, Hamilton-17 depression, NPI) evaluated at baseline and at 12 months. APO was discontinued at night.
Results: At 12 months APO treatment (74.78 ± 24.42 mg/day) resulted in significant reduction in off time (−51%) and no change in AIMS. Levodopa equivalent medication doses were reduced from 665.98 ± 215 mg/day at baseline to 470 ± 229 mg/day. MMSE, NPI, and Hamilton depression scores were unchanged. At 12 months STN-DBS resulted in significant clinical improvement in terms of reduction in daily off time (−76%) and AIMS (−81%) as well as levodopa equivalent medication doses (980 ± 835 to 374 ± 284 mg/day). Four out of 12 patients had stopped oral medications. MMSE was unchanged (from 28.6 ± 0.3 to 28.4 ± 0.6). Hamilton depression was also unchanged, but NPI showed significant worsening (from 6.58 ± 9.8 to 18.16 ± 10.2; $p<0.02$). Category fluency also declined.
Conclusions: Both APO and STN-DBS resulted in significant clinical improvement in complicated PD. STN-DBS resulted in greater reduction in dopaminergic medications and provided 24 h motor benefit. However, STN-DBS, unlike APO, appears to be associated with significant worsening on NPI resulting from long term behavioral problems in some patients.

Subcutaneus apomorphine infusion (APO) and deep brain stimulation of the subthalamic nucleus (STN-DBS) are effective strategies in the management of motor fluctuations and dyskinesias in patients with advanced Parkinson's disease (PD). A few studies have examined neuropsychological and psychiatric changes during APO treatment. Some authors reported an improvement in depressive symptoms,[1 2 5 6] while others[2–4] observed that high doses of apomorphine may, occasionally, lead to hypomania, mania, disinhibition, hypersexuality, and perseveration.

In contrast, numerous studies have evaluated cognitive and neuropsychiatric changes after STN-DBS.[7–12] Many authors reported decreased verbal fluency,[8 13–18] while others suggested that transient or permanent hypomaniac or maniac symptoms, psychosis, and aggressive behaviour may occur in some cases.[7 8 15 19 20] Results are conflicting for mood related items after STN-DBS, and no change as well as improvement[7 9 12 13 17] or worsening have been reported.[15 21–23] Concerns have been raised by a recent report that STN-DBS may increase the risk of suicidal behaviour,[30] although other authors reported less serious effects.[31 32]

One study[24] compared the cognitive effects of APO and STN-DBS after 6 and 12 months' treatment. The authors found no differences in cognitive tests in the APO group (seven patients), but in the DBS group (nine patients) they observed a worsening in phonetic verbal fluency and Stroop naming scores (the latter partially reversible at 1 year follow up).

In this study we evaluated both at baseline and after 12 month follow up, two PD cohorts presenting with motor complications who were offered either APO or STN-DBS. In addition to clinical and cognitive outcome, we also assessed the neuropsychiatric status of the patients using the Neuro-Psychiatric Inventory (NPI).

METHODS

We have prospectively evaluated 13 PD patients who received continuous APO infusion (age: mean 59 years, SD 13; disease duration: mean 10 years, SD 5; Hoehn and Yahr (H&Y) stage ⩾3) and 12 PD patients who underwent STN-DBS (age: mean 60.5 years, SD 6.5; disease duration: mean 12 years, SD 2.45; H&Y stage ⩾3) at baseline and after 12 months' treatment. All patients had been followed at our Parkinson

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; APO, subcutaneous apomorphine infusion; CF, category fluency; CPM, Raven's Coloured Progressive Matrices; CVLT, the California Verbal Learning Test; HDRS-17, Hamilton Depression Rating Scale-17; H&Y stage, Hoehn and Yahr stage; MMSE, Mini-Mental State Examination; NPI, Neuro-Psychiatric Inventory; PD, Parkinson's disease; PF, phonemic fluency; PWL, Paired Word Learning; STN-DBS, deep brain stimulation of the subthalamic nucleus; UPDRS-III, Unified Parkinson's Disease Rating Scale motor examination

Table 1 NPS assessment results

Test	Baseline, mean (SD)	12 Months, mean (SD)	t	z	p
DBS treatment					
MMSE	28.80 (1.78)	29.38 (1.06)	5.5	1.44	0.15
PWL	10.63 (4.28)	9.95 (3.76)	35.0	0.31	0.75
CPM	30.00 (4.85)	31.92 (3.37)	18.5	1.61	0.11
PF	30.67 (7.16)	28.08 (6.43)	14.0	1.38	0.17
CF	43.58 (7.83)	36.58 (10.23)	1.5	2.94	0.00
NPI	6.58 (9.83)	18.16 (10.24)	6.0	2.40	0.02
HDRS	4.83 (2.69)	7.0 (5.2)	13.5	1.73	0.08
APO treatment					
MMSE	28.32 (2.49)	27.58 (4.61)	31.0	0.63	0.53
CVLT	45.62 (9.74)	53.65 (20.36)	7.0	1.18	0.24
Corsi test	4.90 (0.56)	4.25 (1.37)	10.5	1.73	0.08
NPI	10.08 (15.15)	10.92 (11.29)	31.5	0.13	0.89
HDRS	10.00 (7.32)	7.46 (5.98)	16.0	1.51	0.13

The last three columns contain statistical results: differences between baseline and 12 months are significant ($p<0.05$ corrected) only for CF and NPI in the DBS group (CF was not assessed in the APO group).

outpatient facility for many years and presented with motor fluctuations and dyskinesias that could not be controlled with standard oral treatment. They all fulfilled UK Brain Bank diagnostic criteria for PD.

All patients fulfilled CAPSIT-PD (Core Assessment Program For Surgical Intervention in Parkinson's Disease) inclusion criteria for DBS: no dementia, age <70, presence of motor fluctuations and dyskinesia, H&Y stage ⩾3, and change in motor UPDRS score >30% between the off and on states. Exclusion criteria were: presence of atypical features (such as falling, gaze abnormalities, autonomic dysfunction), and significant psychiatric disturbances as well as current treatment with atypical neuroleptics. No formal randomisation was performed, but patients were offered the opportunity to choose between the two procedures; patients chose APO infusion mainly because of the long waiting list for DBS (over 18 months). There were no differences in clinical and demographic features between the two PD cohorts at baseline.

Because of the difficulties that advanced PD patients might experience in performing complex neuropsychology evaluations, we chose to perform additional testing to assess potential treatment specific changes: memory in the APO cohort (we did not expect changes in frontal lobe function compared to previous oral treatment but rather confusion episodes due to the continuous dopaminergic stimulation) and frontal lobe function in the STN-DBS cohort (based on previous literature reports). We therefore performed in both cohorts the following neuropsychological testing at baseline and after 12 months' treatment: Mini-Mental State Examination (MMSE), Hamilton Depression Rating Scale-17 (HDRS-17), and the NPI. In addition, in the DBS group we also assessed verbal fluency (phonemic fluencies (PF) and category fluencies (CF)), Raven's Coloured Progressive Matrices (CPM), and Paired Word Learning (PWL), while in the APO group we administered the California Verbal Learning Test (CVLT) and the Corsi Block Tapping Span test. Neuropsychological assessment was always carried out in the on condition.

Clinical evaluations included: UPDRS score in the morning before the first medication intake (off) and 90 min after medication (on). All patients were treated with a combination of levodopa and dopamine agonists. All dosages were converted to levodopa equivalent doses (1 mg pergolide = 1.5 mg pramipexole = 6 mg ropinirole = 1.5 mg cabergoline = 100 mg levodopa).[33] Off time was calculated on the basis of a 12 h daily chart provided to patients. Patients were asked to fill out the chart on the 5 days preceding the baseline and the 12 month evaluations, and values were averaged. APO was discontinued at night time. STN-DBS was performed using stereotactic surgery with microelectrode recording and macrostimulation following MRI targeting and according to previously published surgical procedures.[34] Due to the size of the two groups, statistical analysis was performed using the Wilcoxon non-parametric test to compare baseline versus 12 month condition in each group with Bonferroni correction for multiple comparisons.

RESULTS

After 12 months, APO treatment (74.78±24.42 mg/day) resulted in a reduction in daily off time (−51% from 2.8±0.8 to 1.4±0.5 h/day; $p<0.001$) and no change in the Abnormal Involuntary Movement Scale (AIMS; +3% from 9.1±2.8 to 9.4±3.1); the Unified Parkinson's Disease Rating Scale motor examination (UPDRS-III) off score was 32.1±7.3 at baseline and 32.9±8.5 at follow up. UPDRS-III scores under treatment did not show any change (19.5±15.6 at baseline and 19.25±14.5 under APO treatment). Levodopa equivalent doses were reduced from 665.98±215 mg/day at baseline to 470±229 mg/day (−29%, $p<0.034$). We found no significant difference in scores of cognitive and behavioural scales between baseline and 12 month evaluations (table 1).

DBS-STN treatment resulted in significant clinical improvement in terms of reduction in daily off time (−76% from 3.1±1 to 0.8±0.7 h/day; $p<0.001$) and AIMS (−81% from 10.2±2.9 to 1.9±1.1; $p<0.001$) as well as levodopa equivalent doses (980±835 to 374±284 mg/day; −62%, $p<0.003$). We found an improvement in UPDRS-III scores off medication with stimulator on (from 33.5±12.9 to 15.7±7; $p<0.003$) and no significant change but a trend for a decrement in the on medication state (from 15.7±7.3 to 12.8±5.9; $p = 0.073$). In these patients we found a significant worsening of both CF and NPI (table 1): we found higher NPI scores in seven out of 12 patients. Reasons for increased NPI were apathy, anxiety, and depression, and one patient showed hypomaniac behaviour. None of these patients had experienced behavioral symptoms requiring psychiatric counseling before DBS.

DISCUSSION

We found that both APO and DBS-STN led to significant clinical improvement in this group of advanced PD patients. Clinically, STN-DBS resulted in greater reduction in dopaminergic medications and off time improvement. Moreover, it provided 24 h motor benefit. However, STN-DBS appeared to be associated with a significant worsening of neuropsychiatric scales resulting in long term behavioural problems in some patients. APO treatment, in contrast, did not affect cognitive or neuropsychiatric functions. A limitation of our study was that patients were not randomised and baseline

differences as well as a non-uniform assessment protocol might have potentially interfered with our conclusions.

Our results regarding continuous APO treatment are in agreement with studies that found no cognitive or neuropsychiatric changes in these patients.[1 24] Some authors[2 3] have reported improvement in neuropsychiatric symptoms after apomorphine using UPDRS-I subscores, although it must be stressed that ratings were based only on clinical impression. More importantly, our inclusion criteria were particularly strict as we considered only patients who were suitable for either APO infusion or DBS surgery.

Conversely, we found a worsening in CF performance in the DBS group in agreement with previous findings from the literature.[7 13–18 24 26] Schroeder and colleagues[29] have recently shown in a PET study that there is a decline in word production when the stimulator is turned on compared to the stimulator off state; these findings would argue against the possibility that a lesion is the basis of verbal fluency deficits in DBS patients. We did not find any change in the remaining cognitive functions we assessed, even though others have reported a higher risk of cognitive deficit in elderly patients and in already compromised patients.[26 27] It is possible that the strict inclusion criteria we used reduced the probability of developing cognitive decline during the 12 month follow-up period.

We found an increase in NPI scores in DBS patients. This finding is novel and is consistent with reports of worsening neuropsychiatric features after STN-DBS.[7 8 15 20 22 28] Our findings confirm that patients who have undergone surgical therapy can develop anxiety, depression, and apathy. Depressive symptoms and apathy seem to be recognised more by caregivers (and operators) than by the patients themselves; in fact NPI scores on these items are significantly higher after 1 year, whereas HDRS scores are higher but do not reach significance. This would also be consistent with increased suicidal risk after DBS.[30]

Some authors have raised the issue that neuropsychiatric changes are directly related to the effect of the stimulator on the limbic system or are secondary to a psychological reaction to lifestyle changes. Indeed, clinical benefit after STN-DBS was greater than with APO in our study, possibly supporting the latter explanation. Nonetheless, we feel that behavioural changes could not be solely attributed to insufficient life adjustment to motor improvement since clinical advantages were also observed during APO infusion. More importantly, the seven patients who showed worsening NPI did not reveal predisposing psychiatric symptoms at baseline.

Finally, our results are in agreement with Alegret and colleagues who did not find any cognitive change in the APO group but did find a decline in phonetic fluency and in Stroop Naming in the DBS group. Using different rating scales, we expanded on their results since we also considered neuropsychiatric features that have been shown to be important, especially in DBS treated patients.

In conclusion, we found behavioural abnormalities during STN-DBS resulting in increased NPI scores. Considering the differences in cost between these two techniques,[35] we believe that additional knowledge may help in selecting appropriate candidates for these procedures. Further studies in larger patient cohorts targeting cognition are warranted to fully assess the benefits and neuropsychiatric risks of these procedures.

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