Different patterns of medication change after subthalamic or pallidal stimulation for Parkinson’s disease: target related effect or selection bias?


Background: Bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) is favoured over bilateral globus pallidus internus (Gpi) DBS for symptomatic treatment of advanced Parkinson’s disease (PD) due to the possibility of reducing medication, despite lack of definitive comparative evidence.

Objective: To analyse outcomes after one year of bilateral Gpi or STN DBS, with consideration of influence of selection bias on the pattern of postsurgical medication change.

Methods: The first patients to undergo bilateral Gpi (n = 10) or STN (n = 10) DBS at our centre were studied. They were assessed presurgically and one year after surgery (CAPIT protocol).

Results: Before surgery the Gpi DBS group had more dyskinesias and received lower doses of medication. At one year, mean reduction in UPDRS off medication score was 35% and 39% in the Gpi and STN groups, respectively (non-significant difference). Dyskinesias reduced in proportion to presurgical severity. The levodopa equivalent dose was significantly reduced only in the STN group (24%). This study highlights the absence of significant differences between the groups in clinical scales and medication dose at one year. In the multivariate analysis of predictive factors for off-state motor improvement, the presurgical levodopa equivalent dose showed a direct relation in the STN and an inverse relation in the Gpi group.

Conclusion: Differences in the patterns of medication change after Gpi and STN DBS may be partly due to a patient selection bias. Both procedures may be equally useful for different subgroups of patients with advanced PD, Gpi DBS especially for patients with lower threshold for dyskinesia.

METHODS

Patients
In 1995, an open prospective study began at our centre to evaluate the results of DBS in patients with advanced PD. The inclusion criteria for surgery were: (a) diagnosis of idiopathic PD according to the core assessment program for intracerebral transplantations (CAPIT) protocol; (b) age between 35 and 75 years; (c) a history of the disease for more than five years; (d) presence of motor complications (motor fluctuations and/or dyskinesias) causing functional disability and not satisfactorily controlled by pharmacological treatment; and (e) levodopa test with an improvement of at least 33% in part III (motor subscale) of the Unified Parkinson’s Disease Rating Scale (UPDRS). The exclusion criteria were: (a) presence of other diseases with poor medium term survival or functional prognosis, or those that increased the surgical risk; (b) dementia or severe cognitive impairment; (c) major psychiatric comorbidity such as severe depression or active psychosis; (d) any other condition compromising the patient’s ability to provide freely given informed consent or to cooperate during surgery or postoperative management; and (e) need for heart pacemaker or presence of any other contraindication for neurostimulation. All patients gave their written informed consent.

Abbreviations: CAPIT, core assessment program for intracerebral transplantations; CT, computed tomography; DBS, deep brain stimulation; Gpi, globus pallidus internus; MR, magnetic resonance; PD, Parkinson’s disease; STN, subthalamic nucleus; UPDRS, Unified Parkinson’s Disease Rating Scale
Initially, patients were not assigned to bilateral Gpi or STN DBS according to predefined criteria. The selection of the target was influenced by the availability of these procedures at our centre and by the outcomes obtained. Gpi DBS was initially introduced as an alternative to pallidotomy, which it then practically replaced, but STN DBS was not definitively incorporated as a treatment option until five years later. From that time on, the STN became the target of choice, although Gpi DBS was still considered for patients with more severe dyskinesias.

For the purpose of the present study, the one year outcomes of the first patients who underwent bilateral Gpi (n = 10) or STN (n = 10) DBS were retrospectively analysed. At the time of the study, 10 patients who had undergone STN DBS had completed a one year follow up. In order to avoid major differences of the effects of the so-called learning curve between the groups, only the first 10 patients to undergo Gpi DBS, who had also completed a one year follow up, were selected for this analysis.

Surgical technique

The stereotactic procedure was performed under local anaesthesia, using the Cosman-Roberts-Well’s frame and computed tomography (CT) or CT-magnetic resonance (MR) image fusion. The anatomical target was defined using the Shaltenbrand and Wharen atlas with the support of a software package (Department of Neurosurgery and Medical Physics, Virgen de las Nieves University Hospital, Granada, Spain). Bilateral 14 mm burr holes were made in the skull just in front of the coronal suture, 3 cm from the midline. The procedure continued as described below.

Gpi DBS

The anatomical target in the posteroventral part of the Gpi was selected 3 mm anterior to the mid-commissural point, 6 mm below the intercommissural line, and 20 mm lateral from the midline. The physiological identification of the definitive target was assisted by microstimulation, considering the stimulation thresholds of the internal capsule and optic tract and the clinical effects on contralateral parkinsonian signs. All patients needed one to two tracks per side. The implanted quadripolar electrode (Model 3387; Medtronic Inc, Minneapolis, MN) was positioned with its middle contacts as close as possible to the location with the lowest threshold for motor benefit and the highest one for adverse effects.

STN DBS

The initial target was 3 mm posterior to the mid-commissural point, 4 mm below the intercommissural line, and 12 mm lateral from the midline. Physiological identification was assisted by microelectrode recordings beginning 11 mm above this theoretical target. Single unit activity along the track was recorded, and the responses to passive and active movements of the contralateral limbs were tested. Most patients needed one to three tracks per side to properly define the boundaries of the STN and identify the sensorimotor region. Microstimulation was used to determine the stimulation thresholds of the adjacent structures, and clinical effects on contralateral parkinsonian signs were tested. After considering all of the information obtained, the definitive target was selected and a quadripolar electrode (Model 3389; Medtronic Inc) was implanted. Macrostimulation was then used to test the clinical effects and thereby position the electrode so that its middle contacts were as close as possible to the location with the lowest threshold for motor benefit and the highest one for adverse effects.

For both Gpi DBS and STN DBS the procedure was then repeated on the contralateral side, and the two electrodes were connected to provisional external leads. The localisation of the electrodes was checked on the day of surgery by plain radiography and MR imaging. All patients underwent stimulation tests within the next few days using the provisional connecting leads and an external pulse generator. A few days later, an internal pulse generator (two Itrel II or one Kineta; Medtronic Inc) was implanted into the subclavicular region under general anaesthesia. The optimal contact(s) and stimulation parameters (frequency, pulse width, and voltage) were selected to obtain the best clinical benefit in both off and on medication states, with subsequent adjustments in the following months as required. The stimulation was continuous in all cases.

Clinical evaluation

All patients were assessed before surgery and every six months after surgery in accordance with the CAPIT protocol in the predefined off medication state (in the morning after 12 hours without antiparkinsonian medication) and best on medication state (period of maximal clinical benefit after usual medication dose), and with the stimulation connected in both situations. The main clinical variables recorded at each assessment were: UPDRS, Hoehn and Yahr staging, Schwab and England Scale, time spent in "off" (from a diary of fluctuations for the preceding week), and CAPIT Dyskinesia Rating Scale (see table 1 for definitions of these scales). Neuropsychological assessment and quality of life studies were also conducted in 10 patients.

The antiparkinsonian medication was optimised in all patients during the months before the surgery. The daily levodopa equivalent dose was calculated on the basis of the following equivalences: 100 mg standard levodopa = 140 mg controlled release levodopa = 10 mg bromocriptine = 1 mg pergolide = 5 mg ropinirole = 1 mg pramipexole = 10 mg selegiline. Regardless of the procedure applied, the medication dose was only changed after the surgery when major clinical changes occurred, ordering the appropriate reduction if there was an intensification of adverse effects (mainly dyskinesias in the on medication state), or the appropriate increase if there was a rise in the severity or duration of off medication periods despite optimal stimulation adjustments. Reduction of medication was never a primary objective of the postsurgical management.

Statistical analysis

The pre and postsurgical variables of both groups (Gpi and STN DBS) were evaluated. For quantitative variables, means and standard deviations were calculated and the one sample Kolmogorov–Smirnov test of normality was applied. The two groups were compared using the Mann–Whitney U test. The magnitude of the change in each variable at one year of surgery was calculated, and pre and postsurgical values were compared within each group by means of Wilcoxon’s signed rank test. A general linear model for repeated measures (analysis of variance, ANOVA) was applied to the main dependent variables (UPDRS III off medication score and levodopa equivalent dose), studying the interactions between the groups. Presurgical predictive factors for percentage change in UPDRS III were analysed by multivariate linear regression, considering interactions according to the type of surgery. All the tests applied were two tailed, and p<0.05 was considered significant. The SPSS 11.0 programme (SPSS Inc, Chicago, IL) was used for the statistical analysis.

RESULTS

Baseline characteristics

The presurgical characteristics of the patients are given in table 1. The distribution of the quantitative variables in each group did not significantly differ from a normal distribution.
Table 1 Presurgical characteristics of and effects at one year after the surgery in the two study groups

<table>
<thead>
<tr>
<th></th>
<th>Gpi DBS</th>
<th>STN DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>One year</td>
</tr>
<tr>
<td>No. of patients</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>7/3</td>
<td>5/5</td>
</tr>
<tr>
<td>Age, years</td>
<td>59.00 (7.23)</td>
<td>62.00 (5.27)</td>
</tr>
<tr>
<td>Duration of disease, years</td>
<td>15.20 (4.19)</td>
<td>14.80 (5.01)</td>
</tr>
<tr>
<td>H and Y stage in &quot;off&quot;</td>
<td>0/10</td>
<td>6/4</td>
</tr>
</tbody>
</table>

Values are means (SD).

* "Change" refers to the mean (SD) of the individual changes in paired comparisons between the baseline and one year evaluations. Minus sign denotes reduction and plus sign increment.

† p value was calculated from paired comparisons between baseline and one year evaluations [Wilcoxon’s signed rank test]. NS, not significant.

H and Y: Hoehn and Yahr Stage (1–5, from lesser to greater severity).

UPDRS: Unified Parkinson’s Disease Rating Scale; total score has a range 0–199, part II (ADL, activities of daily living) score 0–52, and part III (motor) score 0–108.

Adverse events related directly or indirectly to the electrical stimulation appeared only in the STN DBS group (p = 0.086, Fisher’s exact test for comparison of proportions between groups): one patient had dyskinesias and another had paraesthesias, which prevented the programming of a more effective voltage; one patient had apraxia of lid opening and another developed mood change with apathy.

DISCUSSION

The one year outcomes of bilateral Gpi or STN DBS were studied in two cohorts of patients with advanced PD to determine the influence of selection bias on the different patterns of postsurgical medication change. When Gpi DBS became available at our centre in 1995, a high proportion of the patients initially selected for this surgery had severe dyskiniesias, probably influenced by the already established antidyskinetic effect of pallidotomy. STN DBS was not introduced as an alternative approach until five years later,
Subthalamic or pallidal stimulation for Parkinson’s disease

PD.

spread view that STN DBS is the best approach in advanced
below) and could be interpreted as supporting the wide-
differences in the magnitude of changes, discussed
those of other published long term studies1 4 10–23 (although
indirect in these patients. These results are consistent with
improvement showed that the presurgical levodopa equiva-
reduced in proportion to the presurgical severity. However,
the effect on dyskinesias may be partly indirect in these patients. These results are consistent with
those of other published long term studies1 4 10–23 (although
with differences in the magnitude of changes, discussed
below) and could be interpreted as supporting the wide-
spread view that STN DBS is the best approach in advanced
PD.

Nevertheless, and taking into account the presurgical
differences between the patient groups, this study highlights
the point that there were no significant differences in the
motor situation or medication dosage between the groups at
one year after surgery (see fig 1). Therefore, the supposed
advantage of STN DBS in reducing medication may in part be
due to the higher presurgical medication doses of this group.
In other words, the outcomes at our centre indicate that the
difference in the patterns of medication change after Gpi and
STN DBS is at least partly due to a bias in the selection of
patients for one or the other target. Indeed, both procedures
may be equally useful, bringing different types of patient to
an equally favourable motor situation receiving the same
optimal medication dosage. When other variables were
controlled for, our analysis of the predictive factors for motor
improvement showed that the presurgical levodopa equiva-
dent dose was directly related to motor improvement in the
STN group and inversely related to it in the Gpi group.

These findings suggest the hypothesis that Gpi and STN
DBS are distinct procedures which may be useful for different
subgroups of patients with advanced PD. It also appears
that the presurgical levodopa equivalent dose (related to
the dyskinesia threshold, among other factors) may be
an indirect marker of these subgroups. Evidently, this
hypothesis needs to be tested by clinical studies of appro-
riate design and adequate statistical power. In the meantime,
our data indicate that Gpi DBS may also be a valuable
option, especially for patients with a lower threshold for
dyskinesias.

In comparison with other published data,4 10–23 the mean
reduction in the UPDRS III off medication score at one year
was modest in both our groups (35% and 39% in the Gpi and
STN groups, respectively), probably because they were the
first patients to undergo either technique at our centre.
Undoubtedly, an underestimation of the benefits of the
surgery is a drawback of this design, because initial surgical
experience is associated with greater variability in outcomes.
Furthermore, the first patients to undergo a newly available
technique tend to be more severely affected, and surgery is
likely to show lesser efficacy in these patients. At any rate,
their higher presurgical score on the UPDRS III would have
produced a lower percentage improvement for the same
absolute reduction in the score on this scale.

After bilateral STN DBS, the mean reduction in medication
at one year (24%) was also lower in our patients than
reported in other published studies.4 11–21 Although this
difference might also have been influenced by the fact that
they were the first patients treated with this approach, it
could primarily be due to the distinct postsurgical manage-
ment of the patients. At our centre the medication was only
modified when major clinical changes occurred (see
“Methods”), whereas at other centres there was a systematic
reduction or even withdrawal of the medication after STN
DBS.19 21

With respect to the surgical technique, it is to be noted that
microelectrode recordings were only used in the STN surgery,
representing a substantive difference between the two
groups. This may have produced differences in the target
accuracy and, therefore, in the clinical outcomes. At any rate,
both groups in our study showed a comparable degree of
motor improvement.

At our centre DBS surgery has an acceptable safety profile
with a complication rate within the range reported in the
literature. Nevertheless, we had a high rate of delayed
complications related to the devices (25% of patients in our
series during the long term follow up). Although this may be
related to the learning curve, other experienced groups have
reported a similar percentage in long term follow up studies,24
so these complications may have been previously under-
recognised in the short to medium term studies. We observed
a strong tendency in the STN group towards a greater
incidence of adverse events related to electrical stimulation.
This finding may be explained by the smaller size of the STN,
so smaller deviations from the target are more likely to
stimulate adjacent structures.25

The superiority of bilateral Gpi or STN DBS in advanced PD
remains controversial. In terms of medium/long term motor
effects and changes in medication, the available clinical
evidence can be summarised as follows:

Figure 1  Profile plots of the main dependent variables in both groups,
Gpi and STN DBS. Values are estimated marginal means. (A) UPDRS III:
see table 1 footnote. (B) l-dopa equivalent dose: see Methods section.

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The sole randomised comparative study published to date included only four Gpi and five STN patients with a one year follow up, making it difficult to draw definitive conclusions.

The DBS Study Group multicentre study had the largest patient sample, but the study was not designed for direct comparison. At six months, the median reduction in UPDRS III off medication score was 33% in the Gpi DBS group and 51% in the STN DBS group, with a reduction in the medication dose only in the STN DBS group. The patients were assigned to one or the other approach according to the experience and preference of the investigator (several centres only used one of these targets), so that these differences may have partly resulted from the variability in surgical practice, patient selection, or postsurgical patient management among these centres.

Other studies, including the present one, provided a comparative description of the two procedures at a single centre. Krack et al retrospectively analysed outcomes in patients with young onset PD, five stimulated in Gpi and eight in STN. At six months, the STN group showed a greater reduction in UPDRS III off medication score (71% vs 39% in Gpi group), with a mean reduction of 56% in the medication dose. The Gpi group appeared to reflect the same selection bias as in the present study, with more dyskinesias and a lower levodopa equivalent dose (mean difference of 690 mg/day, although this difference was not significant, possibly due to the small sample size). On the other hand, Gpi DBS patients were operated on at a later time, after there had been greater experience with STN DBS. Volkman et al reported outcomes in 11 Gpi DBS and 16 STN DBS patients. At one year, the mean reduction in UPDRS III off medication score was somewhat greater in the Gpi DBS group (67% vs 60% in STN DBS group), whereas the reduction in medication was greater in the STN DBS group (65% vs 16% in Gpi DBS group). Krause et al described the outcomes at one year in five Gpi and 11 STN DBS patients. The results in the Gpi DBS group were disappointing except for alleviation of dyskinesia. According to the authors, this result could be attributed to the stimulation of a different target within the Gpi.

Numerous open studies have evaluated the results of one or the other procedure, but few studies included 10 or more patients with a one year follow up (especially of bilateral Gpi DBS patients). In these studies, the reduction of UPDRS III off medication score ranged from 41% to 67% for bilateral Gpi DBS and from 38% to 67% for bilateral STN DBS. The medication changed little after Gpi DBS, but was reduced by 38–79% after STN DBS, with a total withdrawal of medication in some patients.

The variability in outcomes can be largely attributed to the surgical procedures, but also to differences in the selection and postoperative management of the patients. This hampers the comparison of results, because the relative influence of these factors is not precisely known. In this regard, a greater standardisation of the procedures is desirable in future studies, including the use of specific protocols for changes in medication after the surgery. It is also important to know whether the different patterns of medication change observed by other groups are also partly explained by a patient selection bias. Centres with adequate experience in both techniques may possibly have a selection bias similar to that shown in our study, although other factors may modify its influence on the results.

Further issues to consider in the comparison between Gpi and STN DBS are the effects of the stimulation on non-motor aspects and the incidence of adverse effects. Mood, behavioural, and neuropsychological changes have been more frequently reported with STN DBS than with Gpi DBS, and it has even been suggested that the global results of STN DBS may not be as impressive as previously reported. Evidently, there may be a publication bias because of the greater number of studies of STN DBS. On the other hand, several possible explanations have been proposed for these differences. Mood changes may be more readily induced in these patients because of the smaller size of the STN. It has also been proposed that the marked reduction in or withdrawal of medication after STN DBS may cause some of these changes, calling into question the appropriateness of this strategy.

In summary, there has been no definitive clinical demonstration to date of the superiority of bilateral Gpi or STN DBS in the symptomatic treatment of advanced PD. The most consistent clinical argument in favour of STN DBS has been the possibility of reducing or even suspending the medication. However, this difference may be in part due to a selection bias and to the distinct postsurgical management of the patients. Finally, it is debatable whether a reduction in medication should be the sole criterion of clinical superiority, given the possibility of a higher incidence of mood and neuropsychological changes in patients after STN DBS.

CONCLUSION

Our study suggests that the difference in the patterns of medication change after bilateral Gpi and STN DBS may in part be due to a bias in the selection of patients. In fact, both procedures may be equally useful for different subgroups of patients with advanced PD. Gpi DBS may also be a valuable option for patients with a lower dyskinesia threshold. Further studies are needed to properly evaluate the superiority of one target over the other in the symptomatic treatment of advanced PD.

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