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The medical treatment of patients with Parkinson's disease receiving subthalamic neurostimulation

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ABSTRACT

Introduction: Deep brain stimulation of subthalamic nucleus (STN-DBS) for Parkinson's disease allows for a reduction in medication dosage. Changes in total levodopa equivalent daily dose (LEDD) have been frequently reported, there is little information about changes within the drug classes.
Methods: We retrospectively assessed the changes in antiparkinsonian drugs dosages in 150 patients from one center who had preoperative and postoperative evaluations at 6 months and 3 years. Two long term subgroups with postoperative follow-up till the 5th–6th year ($n = 58$) and 10th year ($n = 15$) were included.
Results: The major modifications in medication dosage occurred during the initial postoperative period. LEDD was reduced by 53.4% compared to baseline at 6 months and 47.9% at 3 years. Fifty six percent and 41.3% of the patients were on monotherapy, 9.3% on no medication at 6 months and 6.7% at 3 years post surgery. Patients on levodopa, or dopamine agonists showed similar reductions. At the 3rd year the oldest group of patients showed a significant decrease in dopamine agonists. The number of patients treated with amantadine was significantly reduced; however the number of patients treated with antidepressants was significantly increased over the first 3 years. Annual medication costs per patient were decreased after the DBS-STN implantation by 61.3% at 6 months and 55.4% at 3 years.
Conclusion: STN-DBS allows for a reduction in the dosage of medication and the costs are similarly reduced. In this cohort different medication groups were reduced to a similar extent. Patients' demographic factors did not play a major role in the selection of treatment.

1. Introduction

The symptomatic treatment of Parkinson's disease (PD) is primarily pharmacological and is prescribed to minimize motor and non-motor symptoms. Medical treatment options include various dopaminergic and non-dopaminergic medications. In many cases, pharmacological therapy is unable to provide satisfactory symptom control as the disease progresses and patients on long term medication may develop disabling side effects [1]. Deep brain stimulation of the subthalamic nucleus (STN-DBS) is an evidence based treatment in advanced stages of PD as it has been shown to improve motor fluctuations, dyskinesia and quality of life better than medication [2]. Furthermore STN-DBS allows for a reduction in medication [3] which is particularly important for patients suffering from side effects of medication such as impulse control disorders or psychosis.

Several studies have demonstrated that the total daily levodopa equivalent daily dose (LEDD) can be reduced following STN-DBS. The short and medium term LEDD changes have been frequently reported, but there are few studies which have examined the timing and time course of the changes in dosage of different antiparkinsonian drugs [4–9].

In this study we analyzed the reduction in dosage of the different catagories of antiparkinson drug over the first 3 years post-surgery in a large cohort. We also analyzed the results for a

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smaller cohorts at both 5 and 10 years compared to baseline. The influence of gender, disease duration at the time of surgery, age at onset and time of surgery were studied in the 3 years cohort. An additional aim of this study was to evaluate the effect of the medication reduction on the cost.

2. Patients and methods

Between 1999 and 2007, 254 patients underwent bilateral STN-DBS for Parkinson's disease (diagnosed according to the United Kingdom Parkinson's Disease Brain Bank criteria) [10] at the Department of Neurology, Kiel. All patients fulfilled the inclusion and exclusion criteria for DBS and underwent bilateral DBS of STN. Surgery was performed with MRI targeting, microrecording and stimulation with 3–5 microelectrodes arranged in Ben's gun under local anesthesia. Subsequently, the permanent electrode (model 3389, DBS, Medtronic Inc.) and the pulse generator (Kinetra, Medtronic, Inc.) were implanted. The final position of the electrode was confirmed with MRI-imaging [11]. The standard pulse settings were 60 μs at 130 Hz. The voltage was adjusted to the patients' individual needs. This retrospective study was approved by the Ethical Committee of the Medical Faculty of the Christian-Albrechts-University.

We recruited 150 out of the 254 patients implanted with STN-DBS. The patients were stratified into subgroups according to their age at the time of surgery (23.3%:≤54 years; 43.3%:55–64 years; 33.3%:≥65 years) age at the disease onset (38%:<45 and 62%:≥ 45 years), disease duration (57.3%:<15 years, 42.7%:≥15 years) and gender (65.3%:males, 34.7%:females).

In addition, fifty eight out of 150 patients were available for follow up at 5–6 year and 15 out of 150 patients were available for at >10 years. The demographic data of this cohort and subgroups are shown in esupp, Table A. There was no significant difference among the groups.

Follow up assessment took place 6 months (6 ± 2 months), 3 years (32 ± 4.7 months), 5–6 years (62 ± 5.6 months) and more than 10 years (12.1 ± 1.6 years) post surgery.

Patients were evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS) in the "off " state (at least 12 h from the last dose of levodopa) and in the "on" (following the administration of one-and-a-half times the morning dose. Postoperatively, they were assessed in 4 conditions (stimulation on/medication off, stimulation off/medication off, stimulation off/medication on, stimulation on/medication on).

Levodopa equivalent daily dose (LEDD) was calculated for each drug according to standard conversions (the daily dose levodopa with carboxylase inhibitor; 0.75 times of controlled release levodopa; 1.3 times of levodopa with entacapone, 1.5 times of levodopa with tolcapone 1.11 times of levodopa/carbidopa intestinal gel (LCIG), 100 times of pramipexole or pergolide or cabergoline or lisuride, 30 times of rotigotine, 20 times of ropinirole 10 times of bromocriptine or apomorphin injection, 5 times of dihydroergocriptin, 2 times of piribedil, 10 times of selegiline and 100 times of rasagiline) [11,12]. The total LEDD was obtained by adding the LEDD of all drugs. Anticholinergics were not expressed as LEDD, because equivalence data are unavailable. All dosages are displayed as daily dosage and in LEDD. We calculated the drug costs based on the German drug cost list ('Rote Liste') and the costs for the highest number of tablets which can be prescribed.

2.1. Statistical analysis

Results are expressed as means ± SD. Pairwise comparison between groups was performed either by Student's *t*-test or by Mann–Whitney U test (according to data distribution), while comparison between different time points for each group was conducted by Wilcoxon rank sum test (statistically significant when $p < 0.01$). In addition, McNemar's chi square test was used for two paired groups with dichotomous variables (statistically significant at the 95% level, $p = 0.05$).

3. Results

3.1. Whole group analysis

LEDD was reduced by 53.4% compared to baseline at 6 months, and by 47.9% at 3 years. Levodopa and dopamine agonists were reduced by the same amount (Table 2): STN-DBS stimulation allowed for a levodopa reduction of 51.9% at 6 months and 46.1% at 3 years. Dopamine agonists were reduced by 57.1% at 6 months and by 52.3% at 3 years (Table 1, Fig. 1). Fourteen (9.3%) of the 150 patients were medication free at 6 months, and in 10 (6.7%) this result was maintained 3 years post-surgery Three patients were on levodopa/carbidopa intestinal gel (LCIG) before DBS. All 3 were able to discontinue LCIG post-surgery. The number of patients on monotherapy preoperatively increased from 41 (27.33%) to 84 (56%: 66 on levodopa, 18 on dopamine agonists) at 6 months and 62 (41.3%: 53 on levodopa, 9 on dopamine agonists) at 3 years.

The number of patients on amantadine significantly decreased from 72 at baseline to 50 at 6 months ($p < 0.05$) and 49 at 3 years. The mean dose of amantadine was also significantly reduced ($p < 0.01$). A substantial reduction of 58% was found for MAO-inhibitors while the reduction in COMT-inhibitors was 49.4% till the 3rd postoperative year. Anticholinergics were almost completely discontinued (Table 1, Fig. 1).

Parkinsonian motor disability (UPDRS III) improved by 25% at 6 months and 15.8% at 3 years. The mean stimulation parameters were slightly increased at the 6 month visit (e-supp, Table B).

The annual medication costs per patient were 7018.5 € at baseline, 2714.9 € at 6th month and 3131.9 € at 3rd year (reduction by 61.3% and 55.4%).

When patients were stratified for age at onset levodopa was reduced by a similar extent in all groups but the reduction in dopamine agonists was significantly more in the older group than in the younger group ($p < 0.001$) (esupp, Table B). The dose of amantadine was also more reduced in the older subgroup ($p < 0.01$). Similar findings were obtained for the three groups separated by age at time of surgery. There were no differences for gender between the two groups. Interestingly, disease duration was not a relevant factor.

3.2. Long term subgroups

The subgroup with 5–6 years postoperative follow up consisted of 58 patients. LEDD was reduced similarly as for the whole group by 51.7% at 6 months and 50.5% at 3 years.

The long term subgroup had a greater reduction in levodopa than the total cohort, but had higher doses of dopamine agonists. By year 5, the percent of reduction in both medications was similar (Table 1).

The mean amantadine dose was also lower, but the reduction was not statistically significant (Table 1).

At 6 months, 7 (12%) patients were medication free, this was sustained in 5 (8.6%) patients at 3 years and 4 (6.9%) patients at 5 years. The number of patients on monotherapy increased to 25 (43.1%: 17 on levodopa, 8 on dopamine agonists) at 6 months, 25 (43.1%: 19 on levodopa, 6 on dopamine agonists) at 3 years and 28 (48.3%: 24 on levodopa, 4 on dopamine agonists) at 5–6 years.

There were 15 patients in the subgroup with more than 10 years follow up. There was a lower reduction in LEDD than for the other groups during the first 3 years and was similar for levodopa and dopamine agonists. There was little variation in the other drugs (Table 2). Three (20%) out of the 15 patients were on levodopa monotherapy at baseline. At 6 months 2 (13.3%) patients were medication free, while 2 (13.3%), 1 (6.7%) and 1 (6.7%) subjects kept this result until the 3rd, 5th and 10th postoperative visit. One patient was prescribed LCIG again following the 6th year follow up visit. Additionally, the number of patients on monotherapy increased to 7 at 6 months (46.7%: 6 on levodopa, 1 on dopamine agonists); 8 at 3 years (53.3%: 6 on Levodopa, 2 on dopamine agonists); 10 at 5–6 years (66.7%: 9 on levodopa, 1 on dopamine agonists) and 11 at the last follow up (73.3%: all on levodopa).

3.3. Non-motor symptom medications

Table 2 shows the number of patients taking neuroleptics and antidepressants. The number of patients treated with neuroleptics was reduced at the 6th month follow up, but was followed by an increase by the 3rd postoperative year and thereafter. The number of patients taking antidepressants increased in the 3 yrs and the 5–6 yrs cohort.

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