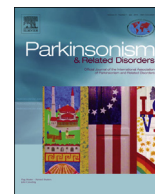




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Short communication

Earlier versus later subthalamic deep brain stimulation in Parkinson's disease

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ABSTRACT

Introduction: Subthalamic nucleus deep brain stimulation (STN-DBS) has been recently compared to a possible “second therapeutic honeymoon” for Parkinson's disease, as it might prevent the development of severe motor complications and lessen the social adjustment associated to disease progression. This study aims to evaluate whether an early surgical treatment could result in better long-term outcomes, comparing the follow-up evolution of 203 parkinsonian patients, treated at different stages of the disease course.

Methods: The retrospective allocation to Early- or Late-Stimulated groups was performed in accordance to disease severity at the time of surgery and motor fluctuations duration. Then, the two groups clinical outcomes were compared after more than 8 years of follow-up by means of the Unified Parkinson's Disease Rating Scale, reporting the overall disability experienced by patients during the entire observational period.

Results: Subjects receiving an earlier STN-DBS showed a sustained improvement in the activities of daily living and motor complications, never reaching the severe levels of disability reported by Late-Stimulated patients at the time of surgical selection. After ≥ 8 years of follow-up the Early-Stimulated group still reported a 28.7% lower impairment in activities of daily living and 43.8% lower duration of waking day spent in OFF compared to their pre-surgical basal scores.

Conclusion: Although the limitation of a retrospective study design should be considered in the interpretation of data, our findings suggest that an earlier STN-DBS treatment might result in a more precious stabilization of motor complications, with beneficial effects on the patient's social and professional life autonomy.

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1. Introduction

Subthalamic nucleus deep brain stimulation (STN-DBS) best clinical results have been reported in Parkinson's disease (PD) patients with younger age, excellent levodopa response, few or no axial motor symptoms and no signs of cognitive impairment [1], while the appearance of non-dopaminergic clinical features may result in a significant limitation of the surgical treatment beneficial effects [2].

It has been suggested that an earlier STN-DBS might prevent the development of severe motor complications, lessening the social adjustment induced by the disease progression and providing a better quality of life [3,4]. These beneficial effects could lead to

additional years of good motor performance which, by prolonging the PD intermediate phase, has been compared to a “second therapeutic honeymoon” [5] or even to a “change of the disease course”, in terms of disability management and patient's autonomy in the activities of daily living (ADL) [6]. Still, there is no general consensus on the optimal timing for STN-DBS, given the possible complications and side-effects of surgery and the lack of long-term comparative data between patients treated at different stages of the disease severity. This report analyses the long-term clinical data of 203 consecutive patients treated with STN-DBS, comparing the outcomes of subjects treated in an earlier or more advanced phase of PD.

2. Patients and methods

All PD patients treated with STN-DBS at our Centre between 1998 and 2012 were considered. Patients were divided into two

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different groups, including in the Early-Stimulation (Early-Stim) group subjects with Hoehn and Yahr stage < 3 in ON-condition and motor fluctuations lasting for ≤ 3 years, in accordance with the inclusion criteria used by Schuepbach et al. [3]; all the other patients were included in the Late-Stimulation (Late-Stim) group. A complete Unified Parkinson's Disease Rating Scale (UPDRS) was performed at baseline (before STN-DBS), both in "OFF-condition" (≥ 12 h after the last levodopa dose) and in "ON-condition" (≥ 40 min after a levodopa challenge dose). UPDRS-III axial subscore was additionally calculated by the sum of items 18, 22, 27–30. Follow-up data were available for 198 patients at baseline (50 Early-Stim/148 Late-Stim), 165 at 1 year (44 Early-Stim/121 Late Stim), 64 at 5 years (19 Early-Stim/45 Late Stim) and 40 at ≥ 8 years (15 Early-Stim/25 Late Stim). Only subjects with follow-up duration ≥ 8 years were included in the long-term analyses. "Clinically important differences" and "minimally important changes" were defined in accordance with literature data [7], using the cut-offs of 3 points for UPDRS-II, 2.5 points for UPDRS-III and 2.3 points for UPDRS-IV. All subjects signed a written informed consent and the local ethical committee approval was obtained.

2.1. Statistical analysis

Mann–Whitney U, Cramer's V and Kruskal–Wallis tests were used for comparisons between groups at baseline, while comparisons at different timelines were performed by means of Wilcoxon rank sum test and a repeated-measures general linear model was used to compare the Early-Stim and Late-Stim outcomes during follow-up. Correlation coefficients were calculated by means of Pearson's test. All analyses were performed using SPSS 21.0, considering 0.05 as the statistical threshold and reporting two-tailed p-values.

3. Results

Considering the entire cohort of patients, 24.6% of subjects fulfilled the Early-Stim criteria. However, the retrospective allocation to Early-Stim and Late-Stim groups demonstrated a significant trend ($p:0.013$) towards a progressively earlier surgical selection: only 14% of subjects in the 1st quartile of STN-DBS patients fulfilled the Early-Stim criteria, while this percentage increased to 16% in the 2nd quartile, 34% in the 3rd quartile and 36% in the last quartile.

At the baseline assessment Early-Stim and Late-Stim subjects showed a similar age at onset (43.80 ± 7.70 VS 43.75 ± 5.71 years; $p: 0.660$) and gender distribution (61.8% VS 59.9% of males; $p: 0.515$) but different disease duration (11.90 ± 2.77 VS 17.19 ± 4.94 years; $p: 0.010$), duration of motor fluctuations (2.52 ± 0.75 VS 9.69 ± 5.16 years; $p < 0.001$), age at surgery (55.70 ± 7.07 VS 60.94 ± 4.42 years; $p: 0.041$), Axial/Med-OFF scores (10 ± 4.3 VS 13.1 ± 4.1 $p:0.045$) and UPDRS-IV scores (7.2 ± 2.2 VS 9.5 ± 2.9 ; $p: 0.041$). Moreover, as reported in Table 1, the two groups had similar LEDD ($p: 0.452$), UPDRS-I ($p: 0.660$), UPDRS-II/Med-OFF ($p: 0.938$), UPDRS-II/Med-ON ($p: 0.225$), UPDRS-III/Med-OFF ($p: 0.897$), UPDRS-III/Med-ON ($p: 0.310$), and Axial/Med-ON ($p: 0.310$) baseline scores.

3.1. Activities of daily living

The UPDRS-II/Med-ON scores showed a similar trend in Early-Stim and Late-Stim subjects during follow-up (Table 1), without long-term significant differences of outcome ($p:0.435$). On the other hand, the Early-Stim patients reported a moderately milder slope of UPDRS-II/Med-OFF scores progression (Fig. 1A), although not reaching the significance threshold ($p:0.110$): a sustained stabilization of ADL score was observed in the Early-Stim group, which reported at the last follow-up evaluation a 28.7% lower ADL

impairment (6.6 UPDRS points) compared to their pre-surgical baseline values ($p:0.028$) and a 31% lower scores versus the pre-surgical disability of Late-Stim group ($p:0.002$). On the contrary, after a similar post-surgical improvement, the group of Late-Stim subjects showed a substantial re-alignment to the baseline scores during follow-up ($p:0.796$; Table 1).

3.2. Motor symptoms

Early-Stim and Late-Stim subjects showed a similar improvement of UPDRS-III motor symptoms after STN-DBS ($p < 0.001$ in both cases), followed by a gradual worsening at 5 and ≥ 8 years (Table 1). The Axial/Med-ON scores gradually increased in both Early- and Late-Stimulated patients (Table 1), without significant differences of outcomes ($p:0.932$), while an initial amelioration of Axial/Med-OFF scores ($p < 0.01$) was observed after surgery in the two groups, followed by a mild progressive worsening during follow-up (Fig. 1B). Moreover, a significant correlation was found between Axial/Med-OFF and UPDRS-II/Med-OFF improvement after surgery ($r:0.612$; $p:0.001$) and between Axial/Med-ON and UPDRS-II/Med-ON scores during follow-up ($r:0.490$; $p:0.015$).

3.3. Motor complications

A significant and long-lasting decrease of UPDRS-IV scores was observed in both Early-Stim and Late-Stim patients after STN-DBS (Fig. 1C), with a comparable long-term outcome ($p:0.278$).

The severity of dyskinesias similarly improved in the two groups, by 71.4% in Early-Stim ($p:0.021$) and 73.1% in Late Stim ($p:0.002$) group, while the percentage of waking day spent in OFF improved ($p:0.042$) only in the group of Early-Stim subjects (-43.8%), reporting a less pronounced amelioration (-26.7%) in the Late-Stim group ($p:0.569$). In both cases the baseline levels of disability were not reached after ≥ 8 years of follow-up.

3.4. Complications and side effects

Considering the entire cohort of 203 patients, no deaths or haemorrhagic events were observed within 30 days after surgery. Three Late-Stim patients reported partial seizures (1.48%), successfully treated with antiepileptic drugs; two Late-Stim patients developed transient postoperative confusion (0.98%), completely resolved within 48–72 h; one Early-Stim patient underwent removal of electrodes and hardware components because of bacterial infection (0.49%) in proximity of the implantable pulse generator.

4. Discussion

Although the sustained and long-lasting efficacy of STN-DBS in the treatment of advanced PD has been extensively demonstrated [8], no general consensus exists on the optimal timing for surgery. Mathematical-based decision models suggest that early STN-DBS may convey greater quality-adjusted life expectancy than delayed procedures [9], and recent evidences proposed that an earlier STN-DBS might improve the clinical management of motor complications responsible for professional limitations and social life impairment [3–6,10].

In this study, we report the retrospective analysis of 203 consecutive subjects treated with STN-DBS at different stages of PD, with the aim of comparing patients receiving surgery at the beginning of motor complications to those treated after several years of disabling dyskinesias and motor fluctuations.

A significant and long-lasting improvement of motor complications was observed in both Early-Stim and Late-Stim patients

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