Self-adjustment of deep brain stimulation delays optimization in Parkinson’s disease

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A R T I C L E   I N F O

Article history:
Received 16 July 2020
Received in revised form 20 January 2021
Accepted 1 April 2021
Available online 11 April 2021

Keywords:
Deep brain stimulation
Parkinson disease
Surgery
Therapy
Programming

A B S T R A C T

Background: Parkinson’s Disease patients undergo time-consuming programming to refine stimulation parameters after deep brain stimulation surgery.
Objective: To assess whether the use of the advanced functions of a patient’s programmer would facilitate programming of deep brain stimulation.
Methods: Thirty patients were randomly allocated to the use of advanced versus simple mode of the patient programmer in this single-centre, prospective, randomized, controlled study. Primary outcome was the number of days required to optimize the stimulation settings.
Results: The number of days required to optimize stimulation was significantly lower in the simple mode (88.5 ± 33.1 vs. 142.1 ± 67.4, p = 0.01). In addition, the advanced mode group had a higher number of side effects (5.4 ± 3.1 vs. 2.6 ± 1.9, p = 0.0055).
Conclusions: The use of the advanced functions of patient programmer delays programming optimization and it is associated with a higher number of side effects. These findings highlight the need for other methods for faster and safer stimulation programming.

Introduction

Deep brain stimulation (DBS) is standard of care for the treatment of refractory motor complications of Parkinson’s Disease (PD) [1,2]. However, patients must undergo a time consuming trial-and-error process to refine stimulation parameters despite standardized protocols developed to optimize this process [3,4].

The Activa® Patient Programmer (Medtronic, Dublin, Ireland) is a remote control device that directly communicates with the implantable pulse generator (IPG). It can be used in simple mode, i.e. the patient can only check the battery status and turn stimulation on/off, or in advanced mode, i.e. the patient can increase or decrease a given stimulation parameter according to a range established by the physician and/or select among different pre-programmed stimulation group settings. We recently showed that self-adjustment of stimulation using this patient programmer allows for fewer in-hospital visits to achieve optimal benefit in dystonia patients in an open-label retrospective study [5].

The aim of this randomized controlled study was to assess whether the use of the advanced mode of the Activa® Patient Programmer streamlines the optimization process of subthalamic (STN) DBS in PD, thus improving the outcome of stimulation in a shorter period and avoiding unnecessary hospital visits.
### Material and methods

Patients with a diagnosis of PD according to the UK PD Society Brain Bank criteria [6], who fulfilled established inclusion and exclusion criteria for STN DBS [7,8] were recruited; the anticipated ability to use the patient programmer in the advanced mode — as determined by clinical judgement — was a study entry requirement. Thirty consecutive PD patients fulfilling these inclusion criteria were recruited at the Toronto Western Hospital (TWH), Toronto, Canada from March 2016 to February 2018 and were followed up to the optimization visit. Written informed consent was obtained from all participants. The study was approved by the University Health Network Research Ethics Board (15–9643.3).

Pre-operative evaluation (including cognitive and psychiatric assessments), DBS implantation, and post-operative management of stimulation and medication were conducted according to the standard of care in place at TWH [4,7,9]. Assessment of impulsivity was based on clinical interview. Unilateral or bilateral simultaneous STN implants were performed in all patients using the standard stereotactic technique adopted at our center [9]. Patients were seen 4–6 weeks after surgery for the first programming visit, and randomization was allocated using www.randomizer.org (an online randomization tool) to simple or advanced use of the patient programmer. Patients and caregivers were explained how to use the patient programmer, and requested to demonstrate this ability during the clinical visit. Patients in the advanced mode were given ranges to perform adjustments in stimulation voltage, frequency or try different stimulation groups, if needed. Patients were given complete freedom to perform as many adjustments deemed necessary. The amount of stimulation patients in the advanced group could adjust was based on the physician’s judgement and expertise, considering each given patient’s clinical picture (evaluating factors such as presence and severity of dyskinesias, early or late programming stage, among others). The number and frequency of following clinical visits were tailored to patients’ needs; e.g. for the evaluation and adjustment of stimulation settings, management of medication, or side effects, and were determined by the physician. Telephone contact did not count as a visit.

Primary study outcome was the number of days required to optimize the stimulation settings (defined as more than 30 days without changing both stimulation and medications). Optimal treatment was considered based on subjective patient satisfaction combined with physician assessment, per standard of care. Secondary outcomes were: i) the number of hospital visits, ii) the occurrence of side effects in the period elapsed between surgery date and last follow-up visit (optimization of stimulation); and iii) the stimulation effect at the last follow-up visit (the comparison of the on-stimulation/off-medication condition to the off-medication condition prior to surgery), measured with the Unified Parkinson’s Disease Rating scale (UPDRS) parts I-IV [10]. Relevant predefined health outcomes for disease status (Hoehn and Yahr scale) [11], subscores of UPDRS IV (items 32 – duration of dyskinesias, 33 – disability related to dyskinesias, 34 – painful dyskinesias, 35 – presence of early morning dystonia and 39 – proportion of the day in the “off” state) and the Parkinson’s Disease Questionnaire (PDQ-39) [12] were also analyzed. Levodopa equivalent daily dose (LED). was calculated according to previous recommendations [13]. Adverse events were classified as related to the surgical procedure, hardware, stimulation or other (e.g., medication changes), for intensity (mild, moderate, severe, disabling/life-threatening, or fatal) and course (transient or persistent). The study was not blinded.

### Statistical analysis

Assuming a mean time to reach the optimization of 16 ± 3 weeks with a desired power of 80% and an α of 5%, a sample size of 15 subjects for each study arm (N = 30 patients) was considered sufficient to detect a difference of at least 20% in the primary outcome. Preoperative variables (demographic and clinical characteristics) and electrode location (distance from each patient’s active contact to the mean location of active contacts on that side) were compared using T-test for unpaired samples, Mann-Whitney test, Fisher exact test or chi-square test as appropriate. Primary and secondary outcomes were compared using T-test or Mann-Whitney test depending on the data distribution whereas comparison of preoperative and optimization status were performed using Wilcoxon signed-rank test. Level of significance was set at <0.05. Analyses were performed using STATA/IC 15.1 software.

### Results

Sixty-three patients were approached for the study and 33 were ineligible or declined, most of the time due to language barrier or anticipated inability/unwillingness to use the patient programmer. Twenty-six of the 30 enrolled patients completed the study. Three patients (20%) from the simple mode group dropped-out because advanced mode was deemed necessary. These patients were significantly impaired by prolonged OFF periods or axial issues affecting patient satisfaction and quality of life, and it was felt the ability to adjust settings in between visits could promote improvement in these areas. One patient from the advanced mode group was excluded due to the occurrence of permanent lower limb dyskinesia resulting from the insertional effect (Fig. 1). Twenty-six patients were analyzed for primary and secondary outcomes (simple mode n = 12, advanced mode n = 14). Baseline characteristics and electrode location are shown in Table 1. The two groups were similar in all the considered features except for LEDD prior to surgery, which was higher in the simple mode group (1684.4 ± 764.7 vs. 942.6 ± 779.2, p = 0.02).

### Study outcomes

The number of days required to optimize was significantly lower in the simple mode (88.5 ± 33.1 vs. 142.1 ± 67.4, p = 0.01); whereas there was no significant difference in the number of hospital visits (5.8 ± 1.2 vs. 6.5 ± 1.3, p = 0.14) (Fig. 2). The total number of side effects was significantly higher in the advanced mode (5.4 ± 3.1 vs. 2.6 ± 1.9, p = 0.0055) (Fig. 2); while the difference in the number of stimulation-induced side effects did not reach statistical significance (1.4 ± 1.1 vs. 0.7 ± 0.8, p = 0.08). Of the 27 events related to stimulation (Suppl Table 1), 19 (70.4%) occurred in the advanced group and were mostly mild (17 mild and 2 moderate). Most of the transient stimulation-induced events were related to high amplitude, and the most frequent event leading to self-adjustment were dyskinesias, but patients could try adjustments for any other symptoms. Although we did not encounter patients or caregivers that expressed they were unable to use the patient programmer to perform adjustments, we considered one patient experience side-effect due to inappropriate use of the programmer (inadvertently turning stimulation off). Two serious adverse events — a syncope episode resulting in a motor vehicle accident and hemorrhage and edema around the path of the electrodes associated with behavioral changes and falls — were reported in the simple mode arm but were unrelated to stimulation or stratification in simple vs. advanced groups (Table 1).
Fig. 1. Study flowchart. DBS, deep brain stimulation; PD, Parkinson’s Disease.
Table 1
Baseline characteristics, pre-operative and optimization scores, electrode location and summary of adverse events (significant differences are bold-typed).

|                        | Simple (n = 12) | Advanced (n = 14) | p valuea |
|------------------------|----------------|-------------------|----------|
| Age (years)            | 60.3 ± 6.9     | 64.4 ± 6.1        | 0.13     |
| Age at disease onset (years) | 50.8 ± 6.1 | 54.9 ± 6.4        | 0.10     |
| Sex                    | 9 M, 3 F       | 11 M, 3 F         | 0.83     |
| Pre-op HY (off-med)    |               |                   |          |
| Pre-op                 | 2.6 ± 0.5      | 2.5 ± 0.5         | 0.54     |
| Optimization           | 2.5 ± 0.4      | 2.6 ± 0.6         | 0.57     |
| Pre-op HY (on-med)     |               |                   |          |
| Pre-op                 | 2.2 ± 0.2      | 2.1 ± 0.3         | 0.83     |
| Optimization           | 2.4 ± 0.3      | 2.4 ± 0.4         | 0.91     |
| LEDD                   |               |                   |          |
| Pre-op                 | 1684.4 ± 764.7 | 942.6 ± 779.2     | 0.02     |
| Optimization           | 662.7 ± 340.3b | 477.7 ± 470.1b    | 0.26     |
| UPDRS I                |               |                   |          |
| Pre-op                 | 2.2 ± 2.1      | 2.0 ± 1.5         | 0.94     |
| Optimization           | 1.2 ± 0.9      | 1.8 ± 1.9         | 0.55     |
| UPDRS II (off-med)     |               |                   |          |
| Pre-op                 | 17.6 ± 6.3     | 17.3 ± 5.5        | 0.90     |
| Optimization           | 8.5 ± 4.1b     | 9.9 ± 5.7b        | 0.68     |
| UPDRS II (on-med)      |               |                   |          |
| Pre-op                 | 5.1 ± 4.0      | 6.8 ± 5.1         | 0.37     |
| Optimization           | 6.2 ± 3.6      | 8.7 ± 5.2         | 0.19     |
| UPDRS III (off-med)    |               |                   |          |
| Pre-op                 | 30.5 ± 9.1     | 36.2 ± 10.0       | 0.14     |
| Optimization           | 18.0 ± 8.5b    | 22.1 ± 11.1b      | 0.32     |
| UPDRS III (on-med)     |               |                   |          |
| Pre-op                 | 13.3 ± 7.0     | 15.9 ± 8.3        | 0.54     |
| Optimization           | 12.1 ± 5.7     | 15.0 ± 6.8        | 0.28     |
| UPDRS IV               |               |                   |          |
| Pre-op                 | 7.9 ± 3.0      | 6.8 ± 3.8         | 0.41     |
| Optimization           | 1.8 ± 1.2b     | 2.7 ± 2.5b        | 0.47     |
| UPDRS IV item 32       |               |                   |          |
| Pre-op                 | 1.3 ± 1.0      | 1.1 ± 1.2         | 0.67     |
| Optimization           | 0.3 ± 0.5b     | 0.3 ± 0.9b        | 0.64     |
| UPDRS IV item 33       |               |                   |          |
| Pre-op                 | 0.8 ± 1.1      | 0.8 ± 1.1         | 0.95     |
| Optimization           | 0.1 ± 0.3b     | 0.1 ± 0.3b        | 0.95     |
| UPDRS IV item 34       |               |                   |          |
| Pre-op                 | 0.2 ± 0.6      | 0.5 ± 1.0         | 0.35     |
| Optimization           | 0.2 ± 0.6      | 0 ± 0             | 0.30     |
| UPDRS IV item 35       |               |                   |          |
| Pre-op                 | 0.7 ± 0.5      | 0.6 ± 0.5         | 0.90     |
| Optimization           | 0.1 ± 0.3b     | 0.4 ± 0.5         | 0.08     |
| UPDRS IV item 39       |               |                   |          |
| Pre-op                 | 1.5 ± 0.5      | 2.1 ± 1.0         | 0.12     |
| Optimization           | 0.4 ± 0.5b     | 0.5 ± 0.5b        | 0.83     |
| PDQ39-SI               |               |                   |          |
| Pre-op                 | 25.8 ± 11.0    | 30.6 ± 14.1       | 0.34     |
| Optimization           | 15.2 ± 10.0b   | 21.5 ± 19.2       | 0.45     |
| Electrode distancec (mm)|             |                   |          |
| R                      | 2.7 ± 1.1      | 3.2 ± 1.0         | 0.70     |
| L                      | 2.9 ± 1.4      | 2.7 ± 1.3         | 0.98     |
| Surgical-related AE (N of events) | 2      | 3            | 0.93     |
| Persistentd             | 2             | 3             |          |
| Transient              | 7 (1 SAE)      | 10             | 0.68     |
| Hardware-related AE (N of events) | 0      | 1            | 0.35     |
| Persistentd             | 0             | 2             |          |
| Transient              | 0             | 2             | 0.18     |
| Stimulation-related AE (N of events) | 4      | 2            | 0.26     |
| Persistentd             | 4             | 2             |          |
| Transient              | 4             | 17            | 0.01     |
| Other AE (N of events)  |               |                   |          |
| Persistentd             | 3             | 15            | 0.005    |
| Transient              | 11 (1 SAE)     | 25             | 0.48     |

Numeric values are mean ± SD. Legend: a = between-group comparison, b = significant difference pre-operative/optimization (p < 0.05); c = mean distance from each participant active contact to mean of all active contacts (from all participants) on that side (obtained using pre- and post-operative T1-weighted MRI to locate DBS electrodes in standard space [Montreal Neurological Institute ICBM 2009b NLIN asymmetric] using Lead-DBS v2.0 software [https://www.lead-dbs.org/]); d = AE persisting by study completion, defined as 30 days after optimization date; AE = adverse events; HY = Hoehn and Yahr scale; LEDD = levodopa equivalent daily dose; L = left side; N = number; off-med = off-medication state; on-med = on-medication state; PDQ39-SI = 39-item Parkinson’s Disease Questionnaire summary index; R = right side; SAE = serious adverse event; UPDRS = Unified Parkinson’s Disease Rating Scale.

The analysis of stimulation effect showed that LEDD, UPDRS II, UPDRS III, UPDRS IV total, UPDRS IV-32, UPDRS IV-33, and UPDRS IV-39 significantly improved in both groups at the last follow-up compared to prior to surgery (Table 1). Motor function (UPDRS III) improved by 41% and 39% in the simple and advanced mode, respectively. Quality of life (PDQ39-SI) significantly improved in the simple mode whereas the improvement seen in the advanced mode did not reach statistical significance (p = 0.0597). Comparison of the final PDQ39-SI scores at optimization visit were not significantly different between simple and advanced mode groups.

Fig. 2. A. Number of days to optimize. B. Number of visits. C. Number of side effects. Numeric values are mean ± 1SD.
(p = 0.45). UPDRS IV-35 improved significantly in the simple mode group (p = 0.0082) only (Table 1). Mean voltage, pulse width and frequency were not significantly different between simple and advanced modes at optimization visit (Suppl Table 2).

Discussion

Our study showed that using advanced functions of the Activa® Patient Programmer in patients with PD did not streamline the optimization process after STN DBS, and in fact patients in the simple mode group reached optimization significantly faster. We had hypothesized patients in the simple mode would take longer to optimize, as physicians could be more cautious with adjustments in this group (due to the lack of patients’ ability to perform adjustments at home). However, advanced mode patients probably performed excessive self-adjustments, delaying the optimization process. There was no significant difference between the two groups in the number of hospital visits to reach optimization, thus meaning that patients allocated to the simple mode underwent more frequent visits since their optimization time was shorter. Furthermore, patients in the advanced mode group were exposed to a higher total number of side effects, albeit most of them were mild and unrelated to the study intervention (i.e. allocation to simple or advanced mode). The number of stimulation-induced side effects was higher in the advanced mode, but the difference did not reach statistical significance. Some of these stimulation-induced side effects can be partly explained by the clinician feeling more comfortable with greater increases in stimulation (i.e. knowing that patient could reduce stimulation at home if needed) but another possible contributing factor was patients’ excessive adjustments of parameters. The reason for a higher number of side effects unrelated to stimulation in the advanced group is unclear. It is however important to note the overall rate of adverse events was higher in our trial compared to observations from previous studies [14–17], which could be related to our standardized and rigorous recording of side effects. Despite these differences, analysis of stimulation effect (comparison of scores at last follow-up to presurgical scores) showed significant improvement of motor performance (UPDRS III) and motor complications (UPDRS IV) in both groups. The motor improvement seen in both groups (41% and 39%) is in line with DBS improvement in the literature [1,18,19]. Although the comparison of all outcome measures (including PDQ39-SI) recorded at optimization visit were not significantly different between simple and advanced mode groups, the within-group comparison of quality of life at last follow-up vs. prior to surgery did not reach statistical significance in the advanced mode group, possibly mirroring the longer time needed for these patients to be optimized. Another possible reason for the lack of significant quality of life improvement in the advanced mode group was the higher number of side effects.

To our knowledge, this is the first trial prospectively assessing whether self-adjustment of stimulation in PD patients reduces the number of days required to optimize. Advanced mode programming has been shown to be time saving in dystonic patients [5], and we hypothesize that stimulation self-adjustment may have a more significant role in diseases in which clinical response to DBS is delayed, such as dystonia and epilepsy. Moreover, it is possible that the fluctuating nature of PD led patients in the advanced mode group to self-perform frequent small adjustments of stimulation, taking longer to meet our criteria for optimization (more than 30 days without changes to stimulation or medications) while not necessarily improving efficacy nor preventing side effects. It should also be acknowledged that PD patients might present a more reactive personality [20], thereby facilitating the adoption of constant self-adjustments with the hope of achieving better disease control. A component of technology addiction cannot be excluded, as seen in PD patients with punding [21]. Finally, it is extremely important to emphasize that the drop-out of 3 patients from the simple mode implies there may be a patient profile in which the ability to self-adjust stimulation is a necessary tool in the DBS journey.

The key strengths of the present study are the prospective nature and randomized evaluation. Limitations of these findings include the occurrence of drop-outs in the simple mode group, lack of blinding, lack of follow-up after the optimization visit, and the baseline difference in LEDD between groups, although we do not think that this difference has played any role in the final findings of our study. Finally, patients in the advanced mode group were not asked how they experienced the possibility of self-adjustments, and we suspect this could have let to burden, or to a feeling of empowerment, depending on different personality traits.

Conclusion

Our findings highlight the need for other approaches that allow for faster (and safer) optimization. Neuroimaging-based programming [22] and adaptive (or closed-loop) stimulation, featuring constant and automatic adjustment of stimulating parameters [23], could potentially streamline and improve the benefits/side effects profile of DBS treatment.

Role of the funding source

This work was supported by the Chair in Neuromodulation and Multidisciplinary care of University of Toronto, Canada and University Health Network, Canada to AF and an unrestricted research grant by Medtronic. The funding source had no role in study design, collection, analysis and interpretation of data.

Full financial disclosures of all authors for the past year

LMO: Funding for travel: Medtronic. MRL, AB, GJBE: none. SKK: Consultancies: Medtronic; Honoraria: Medtronic; Grants: CIHR, Weston, CFI, MH: Grants: Fujitsu Canada. AML: Scientific Director at Functional Neuromodulation; Consultancies: Medtronic, AbbVie, Abbott, Insightec. RPM: Advisory Boards: Medtronic; Grants: Medtronic, travel grants. AF: Consultancies: AbbVie, Medtronic, Boston Scientific, Sunovion, Chiesi farmaceutici, UCB, Ipsen; Advisory Boards: AbbVie, Boston Scientific, Ipsen; Honoraria: AbbVie, Medtronic, Boston Scientific, Sunovion, Chiesi farmaceutici, UCB, Ipsen; Grants: University of Toronto, Weston foundation, AbbVie, Medtronic, Boston Scientific.

CRediT authorship contribution statement

Lais M. Oliveira: Data curation, Funding acquisition, Formal analysis, Writing — original draft, acquisition of data, analysis and interpretation of data, writing of the first draft. Marta Ruiz-Lopez: Data curation, Funding acquisition, acquisition of data, revising manuscript critically for important intellectual content, final approval of the version to be submitted. Alexandre Bouet: Data curation, Funding acquisition, acquisition of data, revising manuscript critically for important intellectual content, final approval of the version to be submitted. Gavin J.B. Elias: Data curation, Funding acquisition, acquisition of data, revising manuscript critically for important intellectual content, final approval of the version to be submitted. Sunil K. Kalia: revising manuscript critically for important intellectual content, final approval of the version to be submitted. Mojgan Hodaei: revising manuscript critically for important intellectual content, final approval of the version to be submitted.
submitted. **Andres M. Lozano:** revising manuscript critically for important intellectual content, final approval of the version to be submitted. **Renato P. Munhoz:** revising manuscript critically for important intellectual content, final approval of the version to be submitted. **Alfonso Fasano:** Conceptualization, Data curation, Conception and design of the study, interpretation of data, revising manuscript critically for important intellectual content, final approval of the version to be submitted.

**Acknowledgments**

Authors are grateful to patients and their families for their participation in this study.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.04.001.

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