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Feasibility of changing for a rechargeable constant current neurostimulator in Parkinson's disease

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ABSTRACT

Background: Little is known about outcome and settings adaptations after replacement of constant-voltage non-rechargeable implantable pulse generator (CV-nrIPG) by constant-current rechargeable IPG (CC-rIPG).

Objective: To determine the feasibility and safety of replacing a CV-nrIPG by a CC-rIPG in Parkinson's disease (PD) and the subsequent outcome.

Methods: A prospective cohort of thirty PD patients, whose CV-nrIPG was replaced by a CC-rIPG in [BLINDED FOR REVIEW] between January 2017 and December 2018 (rIPG group) and 39 PD patients, who underwent the replacement of a CV-nrIPG by the same device in 2016 (nrIPG group), were enrolled in this study. Three surgeons performed the operations. Duration of hospitalization for the replacement as well as the number of in or outpatient visits during the first 3 months after the surgery were recorded. In the rIPG group, we compared preoperative DBS settings and the theoretical amplitude estimated using Ohm's law to the amplitude used at the end of follow-up. We assessed patients' and clinicians' opinion on the patient global functioning after the replacement using Clinical Global Impression score.

Results: Duration of hospitalization (p=0.47) and need for additional hospitalizations (p=0.73) or consultations (p=0.71) to adapt DBS parameters did not differ between the two groups. Neurological condition (CGI score) was considered as unchanged by both patients and neurologists. Final amplitude of stimulation using CC-rIPG was not predicted by Ohm's law in most cases.

Conclusions: Replacing CV-nrIPG by CC-rIPG is safe and well tolerated but require neurological expertise to set the new parameters of stimulation.

KEYWORDS

- Parkinson's Disease
- Deep Brain Stimulation
- Rechargeable Implanted Pulse Generator
- Constant Current Stimulation

SHORT TITLE: Changing for constant current rechargeable IPG

INTRODUCTION

Bilateral subthalamic nucleus deep brain stimulation (STN-DBS) is one of the most efficacious second-line treatments for advanced Parkinson's disease (PD) patients[1]. A major drawback of this technique is the need for non-rechargeable implanted pulse generators (IPG) to be frequently replaced due to battery depletion[2–6]. Furthermore, the new-generation non-rechargeable IPG (nrIPG) have a reduced life expectancy that tends to decrease as a function of the number of replacements[3,4,6]. This induces iterative surgical interventions, which increases the risk of infections and other surgical complications. Indeed, IPG infection risk doubles after IPG replacement in comparison to the first implantation[7]. Furthermore, these complications and the multiplication of IPG changes increase direct and indirect cost and have a negative impact on patients' quality of life[5,8]. Another substantial limitation is the capacity for neurosurgical teams to deal with these growing numbers of IPGs changes. Unavailability of the surgeon at the time of battery running out may also expose PD patients to dramatic rebound of neurological symptoms, potentially leading to life-threatening complications such as pulmonary embolism or aspiration pneumopathy[9].

To overcome these issues, rechargeable constant-voltage IPGs (CV-rIPGs) (Activa-RC*, Medtronic, Minnesota, USA) have been proposed to some PD patients with long life expectancy[10]. More recently, new generation constant-current rechargeable IPGs (CC-rIPG) have been developed and provide even longer battery life expectancy (Gevia* or Vercise*, Boston Scientific, Massachusetts, USA). These new generation IPGs also extend the possibilities of parameters adjustment (allowing smaller pulse width or different frequency on each electrode) that may be useful in patients experiencing axial manifestations such as freezing of gait, dysarthria, or other gait disorders[11–13]. Therefore, it is appealing to propose for PD patients with long life expectancy and able to handle a charger, to switch from a CV-nrIPG (Activa PC*, Medtronic, Minnesota, USA) to a constant-current CC-rIPG (Gevia* or Vercise*, Boston Scientific, Massachusetts, USA). However, this potentially implicates important changes in the way stimulation is delivered (i.e constant voltage versus constant current) and only few studies have assessed the safety, feasibility and clinical consequences of this strategy [14,15]. In particular, the way new parameters of stimulation are implemented remains unknown and notably if the new parameters are predicted or not by Ohm's law ($U=R/I$). The goal of this present monocenter study is to answer these questions.

MATERIAL AND METHODS

Patients

In this monocentric cohort study, we prospectively collected data from consecutive PD patients with STN-DBS, who underwent the replacement of an nrIPG (Activa PC* or Kinetra*, Medtronic, Minnesota, USA) by a constant-current rechargeable one (VERCISE RC™ or GEVIA RC™, Boston Scientific, Massachusetts, USA), in the [BLINDED FOR REVIEW] Hospital from January 2017 to December 2018 (rIPG group). Patients selected for benefiting from a CC-rIPG should have a long-life expectancy promising numerous nrIPG changes in the future, and/or a previous history of surgical site infection and/or a battery lifespan below 2 years. Conversely, we excluded patients who were unable to handle the reloading procedure, mostly because of cognitive impairment. For comparison purposes, we constituted a retrospective reference cohort including all PD patients who underwent in 2016 an IPG replacement using the non-rechargeable device (Activa PC*, Medtronic, Minnesota, USA), at a period when rechargeable devices were not available in our center (nrIPG group). All nrIPGs were used in CV mode only. The protocol was approved by the local ethics committee of [BLINDED FOR REVIEW]. All patients gave informed consent for the procedure.

Surgical procedure

Three different surgeons realized the replacement interventions. Patients undergoing IPG replacement were positioned comfortably supine and the IPG was changed under local anesthesia.

Data collection

The following items were collected: general patients' medical background; age at PD onset; age at inclusion; disease duration; deep brain stimulation duration; history of DBS device infection, or material dysfunction; total number of IPGs replacements. The duration of hospitalization to perform IPG replacement as well as the number of in or outpatients' visits related to IPG replacement or to adjust stimulation parameters during the first 3 months after surgery were recorded. In the rIPG group, we additionally assessed, 3 months after the IPG change, patients and neurologists opinion on patients neurological condition using the Clinical Global Impression (CGI) Improvement scale[16]. The score ranges from 1 (very much improved) to 7 (very much worse), 4 meaning "no change". In addition, patients evaluated the convenience of routine recharging by a specific score ranging from 1 (very cumbersome) to 5 (very simple) as well as the comfort and aesthetic provided by CC-rIPG with a similar score ranging from 1 (very uncomfortable) to 5 (very comfortable)[17].

DBS settings adaptation procedure

Pre-operative ACTIVA PC™ parameters were recorded. To guide the adaptation of DBS settings after the replacement of CV-nrIPG by CC-rIPG we first measured the impedances of the contacts used via the Bionic Navigator™ version 2.0.3 software of VERCISE RC™ device or the Neural Navigator™ version 2.0.0 software of GEVIA RC™. We then calculated a "theoretical amplitude" by using Ohm's law (*U/R=I*). This theoretical amplitude was applied to the IPG immediately after replacement without changing the contact of stimulation, frequency and pulse width. If the benefit on motor symptoms was not satisfying or if patients experienced side effects (paresthesia, oculomotor disorders, pyramidal tract involvement manifestations notably) the neurologist modified first the amplitude of stimulation, then other parameters if necessary without any restrictions (pulse width, frequency, contacts or mode of stimulation). DBS parameters at the end of the 3 months follow-up for both the rIPG and the nrIPG cohort were subsequently recorded and compared to the immediate post-operative parameters. No concomitant modification in antiparkinsonian medications was realized for all patients included in the study during the 3 months follow-up.

Statistical analysis

Categorical variables were expressed as number (n) and percentage. Quantitative variables were expressed as means ± standard deviation, median + first and third quartile. The hypothesis of normal distribution of quantitative variables was tested using the Kolmogorov-Smirnov and graphically confirmed with a histogram. Categorical variables were compared using the Chi 2 test or Fisher's exact test when the conditions of application of Chi square test were not met. Quantitative variables were compared between cohorts using the nonparametric test of Wilcoxon as the hypothesis of normality of distribution was not verified. The search for a correlation between quantitative variables was carried out by calculating the spearman correlation coefficient. Paired comparisons of continuous variables were conducted using the non-parametric signed rank test. The statistical tests were bilateral, and the level of significance was set to 5% ($p < 0.05$). Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc, NC).

RESULTS

Patients' characteristics

From January 2017 to December 2018, 30 patients underwent the replacement of non-rechargeable ACTIVA PC™ IPG by VERCISE RC™ or GEVIA RC™ rechargeable devices.

39 patients benefited from a replacement of CV non-rechargeable device (ACTIVA PC^{TM} or KINETRA) by an ACTIVA PC^{TM} in 2016. In that series, the main reason for choosing a rechargeable device was a large number of estimated device changes in the future because of the long-life expectancy of the patient (80 %). Less frequently a history of device infection (13.3 %) or a particularly short battery lifespan below 2 years (6.7%) were the other reasons for taking this decision. 69 patients received a CV-nrIPG during the study period, either because of the existence of exclusion criteria, either because they preferred a CV-nrIPG to a CC-rIPG. Patients were significantly younger at the time of IPG replacement in the rIPG group in comparison to the nrIPG cohort ($p<0.01$). DBS duration ($p<0.01$), age at disease onset ($p<0.01$) and the mean number of previous IPG replacement ($p=0.028$) were lower in the rIPG group (Table 1). 3 patients from the nrIPG group required IPG change because of device lodge infection and 1 because of hardware failure. By contrast, all IPG replacements from the rIPG device group were performed for end of life battery. There were no statistical differences between groups regarding the other clinical characteristics, namely sex ratio, history of device infection, disease duration or material dysfunction (Table 1).

Patient's management and outcome at 3 months

The duration of the hospitalization for device replacement was not statistically different between the two groups ($p=0.47$). During the 3 months follow-up, 5 patients of the rIPG cohort and 5 of the nrIPG group required rehospitalization for parameters adjustments or rechargeability issues ($p=0.73$). Eleven patients from the rIPG cohort and 16 from the nrIPG group required one or more additional consultations to adjust DBS parameters within the first weeks following surgery ($p=0.71$) (Table 2). Furthermore, the number of outpatient visits ($p= 0.64$) and the duration of rehospitalization needed for parameters adjustment did not differ between groups ($p=0.25$).

Patients' and clinicians' acceptance and tolerability

At 3 months, median neurologist CGI-Improvement score in the rIPG group was 4 +/- 0 while median patient CGI-improvement score was 4 +/- 1, meaning no change. Median patient score assessing the convenience of the recharge procedure was 5 +/- 2 and the median patient comfort score was 5+/- 1.75, indicating a very good tolerance and acceptability of rIPG to the patients.

Complications and adverse or unanticipated events

Apart from one patient from each cohort who presented a superficial infection of the IPG lodge resolving under antibiotherapy, no serious adverse event related to surgery was noted during the follow-up period in the two groups. No deep surgical site infection (pocket) or hardware failure leading to IPG removal was observed (Table 2).

DBS parameters adjustments

At the end of the follow-up period in the rIPG group (60 electrodes), the amplitude was the only parameter modified in 37 electrodes (61.7%) (Table 3). This amplitude adjustment was +/- 5 %, +/- 10 %, +/- 20% or above 20 % of the amplitude estimated from Ohm's law in, respectively, 8 (21.6%), 3, (8.1%), 10 (27%) and 16 (43.3%) of the cases. Overall the median amplitude was significantly lower than the median theoretical amplitude calculated using the Ohm's law (3.5mA +/- 1 versus 4.22mA +/- 1.22; $p<0.01$) On the remaining 23 electrodes (42.7%) of the rIPG cohort, adjustments performed during the follow-up period concerned the mode of stimulation for 5 electrodes (2 electrodes programmed in monopolar mode were changed to double monopolar mode, 2 electrodes from monopolar mode to triple monopolar stimulation and one electrode programmed in bipolar was switched to a monopolar mode of stimulation). In addition, the contact used for 4 electrodes was modified and frequency and/or pulse width were changed for 14 electrodes (Table 3).

At the end of the follow-up period, 8 rIPGs (26.6 %) were programmed using unique (26.6 %) or combined (10 %) specific functionalities of the VERCISE RC™ or the GEVIA RC™ devices, namely pulse width stimulation shorter than 60 us (4 IPGs), unequal repartition of the current delivered in multiple contact stimulation (2 IPGs) and delivery of different frequencies of stimulation on each electrode (5 IPGs). Regarding the settings of the 78 electrodes from the nrIPG group, no modification was made for 63 electrodes (80.7%) whereas 1 patient needed a change in the contact used (2.6%), another one a change in pulse width and 8 patients (13 electrodes) a modification of stimulation intensity (16.7%).

Regarding the impedance of the rIPGs [748-1007 Ohms] we identified an association between this factor and the amplitude of stimulation. For a given electrode, the higher the impedance of the active contact was, the smaller the difference between the theoretical amplitude calculated using Ohm's law and the amplitude delivered was (Spearman's rank correlation coefficient -0,83 ($p>0.001$) for the group of electrodes localized in the left subthalamic nucleus and -0.72 ($p>0.0001$) for the group of electrodes localized within the right subthalamic nucleus). In other terms, the closer the impedance was to 1000 Ohms, the

more effective was the Ohm's law for predicting the final amplitude. Impedances had no influence on the adjustment of frequency, pulse width or mode of stimulation.

DISCUSSION

Key results

Our work pointed out that changing from a CV-nrIPG for a CC-rIPG is feasible with a high level of both clinicians' and patients' satisfaction. We also demonstrated that strictly following Ohm's law was not an effective strategy to adapt the DBS settings after surgery. A quarter of patients benefiting from a replacement by a CC-rIPG were using new devices specificities to better control persistent motor symptoms

Relevance of the findings

The present study is, to our knowledge, the second having analyzed the practical issues of the replacement of CV-nrIPG by a CC-rIPG in PD. CC stimulation reduces current fluctuations seen with CV stimulation[18], which are directly related to impedances variations[19]. This difference is thought to bring some benefits in terms of clinical outcome, but only one study has assessed the effect of switching from CC to CV stimulation in movement disorders, and it only included 13 PD patients[14]. Our work demonstrates that this procedure is technically feasible and does not increase the duration of hospitalizations nor the number of in or out-patient visits for parameters adjustment. Interestingly, we were able to include in our study more than a third (39/99) of all the patients requiring an IPG replacement, meaning this procedure could be potentially applied to a large number of patients in a clinical setting. Furthermore, patient's opinion regarding their neurological condition, the easiness of the recharging procedure and the comfort of the new device (smaller than the previous non-rechargeable one) indicated a high level of satisfaction in line with previous reports[10,17].

In our study, patients in whom a switch from nrIPG to rIPG was performed were significantly younger. This reflected the apprehension we had, when the study was launched, that older patients might experience difficulties to manage rechargeable systems. The main objective of this strategy is to limit the number of IPG replacements and, conversely, the high risk of device infection that may lead to dramatic complications in advanced PD patients if the system needs to be removed. Indeed the risk of infection for the initial DBS surgery is comprised between 1.2 and 6.2 %[7,20–27] but rises up to 20 % for subsequent IPG replacements[4,7,23,28]. Limiting such complication also induces major cost cut. Indeed the cost for a "simple" antibiotherapy with the preservation of the IPG after infection is of 9500 Euros

but rises to 38 700 Euros for antibiotherapy followed by IPG change[8]. And this does not consider the consequences for the patient in terms of stress, days off work or neurological manifestations worsening.

The other major interest of switching from a nrIPG to a rIPG is to limit the expenses and inconvenience of repeated IPG replacements. Two recent studies have shown that using rIPG allows a cost-saving of 60 000 dollars in 9 years[10].

Furthermore, the use of CC-rIPG dramatically diminishes the risk of unexpected battery discharge and its consequences. Indeed, sudden discharge of IPG battery had been observed in nearly a third of our CV-nrIPG cohort. Conversely, no patient from the CC-rIPG group experienced, after the replacement, complete battery discharge, meaning a good understanding of the recharge procedure.

More importantly, the present work gives important clues on how stimulation parameters have to be modified when performing such switch of IPG model. We have demonstrated that Ohm's law is not sufficient to guide stimulation parameters optimization. Indeed, amplitude was the sole parameter modified in 37 electrodes but fits strictly to Ohm's law prediction in only 8 electrodes (5% interval of the amplitude determined using Ohm's law). For most patients (43.3 %), final amplitude was even above 20 % of this estimated amplitude. However, while amplitude estimated by Ohm's law did not reflect the amplitude at 3 months in many cases, this is virtually the only estimation of post-operative amplitude that can be easily used in routine clinical practice for the very first programming after replacement. We demonstrated that higher impedance of the active contact was associated with a smaller difference between theoretical and final amplitude, meaning patients undergoing a replacement from a CV to a CC IPG presenting low impedance of the active contact should be carefully monitored after the surgery. In any case, subsequent reevaluations performed in a consultation or during postoperative hospitalization stay will permit to adjust the intensity of stimulation to adequately control PD motor symptoms. This demonstrates the need for experienced neurologists' involvement to perform such change.

Otherwise, it is of interest to note that some patients implanted with a constant current rechargeable device required more important changes of DBS settings, including new mode of stimulation or modifications in the contact used. The widen possibilities of parameters adjustments (lower pulse width, differential frequencies, current steering) offer by new generation CC-rIPG were, in particular, used in the present study to tackle difficult-to-manage patients, notably those with axial signs but also persistent motor fluctuations[29,11,13]. In coherence with these hypotheses, a quarter of subjects implanted with a CC device were using

specific functionality of Boston's IPGs in our study, essentially shorter pulse width and lower frequency of stimulation. Finally, it is important to note that, whereas all patients from the CC-rIPG required DBS settings adaptation, 19.3% of patients receiving CV-nrIPG also needed a modification of their DBS parameters.

Strengths and limitations of the study

The present study is, to our knowledge, the largest one, having analyzed the feasibility and practical issues of the replacement of CV-nrIPG by a CC-rIPG in PD. However, the sample of the study remains relatively small, and we may have lacked power to detect small differences between the two groups, especially regarding the rare adverse events or to identify association between the impedances of active contacts and the DBS settings adjustment other than amplitude. Additionally, the inclusion criteria we used in this work may have represented a potential selection bias. Indeed, conversely to the patients included in the prospective cohort and implanted with a CC-rIPG who were relatively young, the historical CV-nrIPG cohort gathered all the patients who undertook and IPG replacement for the year 2016, including older patients with a higher number of IPG changes. This later group might have been more likely to experience replacement surgery side effects as well as to have required more follow-up consultations or higher rehospitalization rate. It is also important to note that the follow-up was also limited to 3 months, preventing us from drawing conclusion on the long-term benefits of such a strategy. Future larger and longer scope study would be needed to confirm our findings and to provide practical guidelines for parameters adjustment following replacement of a CV-nrIPG by a CC-rIPG.

CONCLUSION

The present study demonstrates the feasibility and good outcome after such a procedure. This said, it is of major importance to stress that such approach requires a strong involvement of the neurological team and cannot "only" rely on the neurosurgical team because of the needed adjustment.

Disclosure of interest

The authors declare no conflict of interest

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Table 1. Patients' clinical characteristics at baseline

	CC-rIPG group January 2017 - December 2018	VC-nrIPG group January 2016 - December 2016	p value
Number of patients	30	39	/
Type of device	GEVIA RC n = 19, VERCISE RC n= 11	ACTIVA PC n= 39	/
Sex ratio H/F	50%	69.2%	(p=0.10)
Mean age at the time of device replacement (years)	59.32 [50.16 - 68.48]	68.22 [61.57 - 74.77]	(p< 0.01)*
Mean age at the time of disease onset (years)	40.86 [32.7 - 49.02]	48.37 [40.93 - 55.81]	(p< 0.01)*
Mean disease duration at the time of device replacement (years)	18.5 [13.4 - 23.6]	19.8 [14.26 - 25.39]	(p=0.30)
Mean duration of DBS at the time of device replacement (years)	6.18 [2.41 - 9.95]	9.61 [5.84 - 13.38]	(p< 0.01)*
Median number of IPG replacements	1 [1 - 2]	2 [1 - 3]	(p=0.028)*
History of previous device infection	DBS implantation : 6.6% (n=2)	DBS implantation : 2.6% (n=1)	(p=0.72)
	After IPG replacement: 6.6% (n=2)	After IPG replacement : 7.7% (n=3)	
History of unexpected battery arrest	3.3% (n=1)	28% (n=11)	(p< 0.01)*
History of IPG dysfunction	6.6% (n=2)	10.3% (n=4)	(p=0.69)

Table 2. Patients' clinical outcomes after 3 months of follow-up

	CC-rIPG group January 2017 - December 2018	VC-nrIPG group January 2016 - December 2016	p value
Number of patients	30	39	/
Mediane duration of hospitalization to perform replacement (days)	3 [2 - 5]	2 [2 - 4]	p=0.47
Number of patients rehospitalised during the 3 months of follow-up	5 (16.7%)	5 (12.8%)	p=0.65
Median duration of rehospitalization stay (days)	5 [4 - 6]	10 [6-11]	p=0.25
Number of patients requiring consultation during the follow-up	11 (36.67 %)	16 (41.03%)	p=0.71
Total number of consultations performed during the follow up	15 (0.5 per patient)	22 (0.56 per patient)	p=0.64
Infection of IPG lodge	n=1 (3.3 %)	n=1 (2.7 %)	p=1
Haematoma	n=0	n=0	p=1
Surgical issue requiring IPG removal	n=0	n=0	p=1

Table 3. Change in DBS settings following IPG replacement

	Number of electrodes (CC-rIPG cohort)	Percentages	Number of electrodes (CV-nrIPG cohort)	Percentages
Change in the mode of stimulation	5	8.3%	1	1.8%
Change in the contact used	4	6.7%	1	1.8%
Pulse width change only	4	6.7%	2	2.6%
Frequency change only	6	10%	0	0%
Pulse width and frequency change	4	6.7%	0	0%
Amplitude change only	37	61.6%	8	10.3%
No change	/	/	66	84.7%