



Decreasing battery life in subthalamic deep brain stimulation for Parkinson's disease with repeated replacements: Just a matter of energy delivered?

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ABSTRACT

Background: People with Parkinson's disease (PD) treated with deep brain stimulation (DBS) with non-rechargeable implantable pulse generators (IPGs) require elective IPG replacement operations involving surgical and anesthesiologic risk. Life expectancy and the number of replacements per patient with DBS are increasing.

Objective: To determine whether IPG longevity is influenced by stimulation parameters alone or whether there is an independent effect of the number of battery replacements and IPG model.

Methods: PD patients treated with bilateral subthalamic DBS were included if there was at least one IPG replacement due to battery end of life. Fifty-five patients had one or two IPG replacements and seven had three or four replacements, (80 Kinetra[®] and 23 Activa-PC[®]). We calculated longevity corrected for total electrical energy delivered (TEED) and tested for the effect of IPG model and number of previous battery replacements on this measure.

Results: TEED-corrected IPG longevity for the 1st implanted IPG was 51.3 months for Kinetra[®] and 35.6 months for Activa-PC[®], which dropped by 5.9 months and 2.8 months, respectively with each subsequent IPG replacement ($p < 10^{-6}$ for IPG model and $p < 10^{-3}$ for IPG number).

Conclusions: Activa-PC[®] has shorter battery longevity than the older Kinetra[®], battery longevity reduces with repeated IPG replacements and these findings are independent of TEED. Battery longevity should be considered both in clinical decisions and in the design of new DBS systems. Clinicians need accessible, reliable and user-friendly tools to provide online estimated battery consumption and end of life. Furthermore, this study supports the consideration of using rechargeable IPGs in PD.

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Introduction

Deep brain stimulation (DBS) is an important therapeutic modality for Parkinson's disease (PD) [1,2], essential tremor (ET) [3] and dystonia [4]. When these movement disorders respond sub-optimally to oral medications this treatment allows continual therapy and potentially much improved symptom control [5,6]. A

programmable implantable pulse generator (IPG) in the chest wall delivers pulsatile electrical stimulation to the brain via electrodes implanted in the subthalamic nucleus (STN), internal globus pallidus (GPi) or ventral intermediate nucleus of the thalamus (Vim) [6]. With conventional non-rechargeable batteries, the IPG needs to be replaced electively before the battery reaches the end of its life. The first DBS implantations were performed over 20 years ago and there are now an increasing number of patients that have already undergone multiple IPG replacements, many of whom are elderly with multiple comorbidities. If the arguments for DBS implantation earlier in the course of the disease [7] are applied, the number of IPG replacements per patient may rise. For each additional

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procedure there is a risk of infection, which increases with repeated battery replacement operations [3,8], as well as other surgical or anesthesiologic complications [8–10].

Reliable estimation of IPG longevity is clinically important. Overestimation of battery life risks unexpected battery failure, which causes significant worsening of the clinical state often with severe patient discomfort. In extreme cases it may cause parkinsonism-hyperpyrexia syndrome, a potentially fatal condition similar to neuroleptic malignant syndrome [11–19]. Underestimation results in increased patient anxiety and more frequent hospital visits and surgical replacement procedures, resulting in increased costs and risk of complications.

Our group and others have reported that Activa-PC[®] (Medtronic, Minneapolis, MN, USA) are replaced at an earlier time after implantation than Kinetra[®] IPGs [20–23] and that battery longevity declines with each repeated IPG replacement [20,21,23]. Possible explanations proposed included changes in DBS settings, technical differences in the IPG models and patient and hardware changes over time. The aim of this study was to determine whether changes in DBS settings could explain the decrease in battery longevity with repeated IPG replacements and the difference in longevity between IPG models. We performed a retrospective study in a large cohort of PD patients treated with bilateral STN-DBS that had undergone one or more IPG replacements.

Methods

We identified all PD patients treated with bilateral STN DBS from the database of DBS patients followed up at the Movement Disorders Institute, Sheba Medical Center who had reached the end of battery life with at least one Kinetra[®] or Activa-PC[®] IPG. In our practice we have remained solely with voltage control for all patients with Activa IPGs.

IPG longevity was defined as the period of time between IPG implantation and IPG removal. In patients with their first IPG, the IPG was first switched on within 1–2 weeks after surgery. The timing of battery replacement operations was guided by the manufacturer's recommendations (ERI 2.44 V for Kinetra[®] and 2.6 V for Activa-PC[®]) or EOL (end of life).

The local ethics committee approved the study and waived the need for obtaining informed consent as the study was retrospective and anonymous.

We review patients at least 3 times a year once their parameters have been optimized post operatively. We only change their parameters if patients complain or if there is a clinical suspicion of adverse effects or loss of effect.

In our clinic, as is common practice, stimulation impedances are regularly and routinely monitored to identify open or closed circuits and recorded when abnormal. We therefore followed the convention of assuming the impedance to be 1000 Ω [26,27]. Since stimulation mode influences impedance, we attempted to control for these modes, see Supplement for details.

Electrical calculations

Differences in stimulation parameters (voltage, pulse width, frequency and mode) result in different battery drain rates. Intensity of DBS therapy is represented by the total electrical energy delivered (TEED), defined by Equation (1) below [24,25]:

$$TEED = \frac{V^2 \times PW \times f}{Imp} \times 1 \text{ sec} \quad (1)$$

Abbreviations: TEED – total electrical energy delivered (μJ), V –

voltage (V), PW – pulse width (μs), f – frequency (Hz), Imp – impedance (Ω).

For every IPG we calculated the average TEED for each electrode separately at two time points: (1) soon after DBS implantation or IPG replacement after parameter stabilization and (2) at the last telemetry reading prior to IPG replacement. The TEED and stimulation parameters are presented in Table 1.

Differences in stimulation parameters affects battery drain with increasing energy delivered resulting in decreased battery longevity. In order to test for the effect of IPG number (i.e., the number of previous replacements) and the difference between IPG models beyond the effect of changes in stimulation parameters we controlled for this confound. We created a model to predict battery longevity using the 'trendline' function in Microsoft Excel 2016 based on the data from the largest subgroup (the first IPG per patient, Kinetra[®] only). We tested exponential, inverse and power functions. The best goodness of fit, ($R^2 > 0.57$), was obtained by using a power function, see Fig. S2, giving the following equation:

$$Longevity_{pred} = 543.36 \times TEED^{-0.422} \quad (2)$$

TEED was corrected for by first determining the ratio between the observed battery longevity and that predicted by the TEED, which we termed the longevity index, according to Equation (3) below:

$$Longevity_{index} = Longevity_{obs} / Longevity_{pred} \quad (3)$$

The longevity index gives a measure by which the observed battery longevity differed from the predicted longevity for the measured TEED, according to the observed TEED battery relationship for Kinetra[®] IPGs (first implantation only). This value was then multiplied by the predicted longevity (51 months) for the average TEED of the whole sample (271 μJ), derived from Equation (2), to give an estimation of longevity for each IPG had the TEED been the same for all IPGs, see Equation (4) below:

$$Longevity_c = 51 \times Longevity_{index} \quad (4)$$

The stars in Fig. S3 graphically illustrate the method of correcting for TEED variations across IPGs.

Statistical analysis

We used this value as the outcome measure for statistical analysis, which we performed in IBM SPSS Statistics 19, using the linear mixed models model (LMM) with IPG number as a within subject repeated measure. We used the same statistical model to test for differences in demographic and clinical characteristics for the model type and number of IPG replacements by designating gender, patient age and disease duration (at the time of implantation of the first IPG) as the outcome measures. We also used the LMM to test the effect of model and IPG number on the uncorrected battery longevity and then included TEED as a covariate.

Results

Sixty-nine PD patients (43 male) after one to four IPG replacements, in total 125 IPGs, were identified. Nine IPGs were excluded from analysis due to IPG model other than Kinetra[®] or Activa-PC[®]. Another 13 IPGs were excluded due to incomplete medical records or early IPG removal due to infection or electrode misplacement. In total, data from 80 Kinetra[®] and 23 Activa-PC[®] IPGs from 62 PD patients (37 male), who were 59.7 ± 11.1 years-old and 12.6 ± 8.9 years since their diagnosis of PD at their initial DBS operation, were analyzed. Thirty patients had one IPG replacement,

Table 1
Stimulation Parameters and IPG longevity by IPG number and model.

IPG number	IPG model	N	Amplitude (V)	Pulse Width (μ s)	Frequency (Hz)	TEED (μ J)	IPG longevity (months)
1	Kinetra [®]	55	3.13 \pm 0.57	65.2 \pm 12.2	157.5 \pm 25.3	241 \pm 134	57.6 \pm 14.1
	Activa-PC [®]	7	3.25 \pm 0.89	67.9 \pm 16.6	148.6 \pm 20.6	256 \pm 135	36.8 \pm 9.9
2	Kinetra [®]	22	3.25 \pm 0.62	66.8 \pm 15.2	160.6 \pm 23.1	288 \pm 190	47.3 \pm 14.5
	Activa-PC [®]	10	3.37 \pm 0.71	69.0 \pm 11.1	147.0 \pm 23.1	259 \pm 106	38.1 \pm 11.7
3	Kinetra [®]	2	4.35 \pm 0.57	60.0 \pm 0.0	180.0 \pm 0.0	519 \pm 251	30.7 \pm 14.0
	Activa-PC [®]	5	3.15 \pm 0.49	81.0 \pm 27.8	176 \pm 8.9	322 \pm 70	26.0 \pm 6.1
4	Kinetra [®]	1	4.33	75.0	180.0	524	31.6
	Activa-PC [®]	1	4.75	60.0	180.0	696	15.8
Model effect			NS	NS	NS	NS	$p < 10^{-4}$
IPG number effect			$p < 10^{-6}$	NS	$p < 10^{-4}$	$p < 10^{-6}$	$p < 10^{-5}$

Abbreviations: IPG – implantable pulse generator. N - number. TEED – total estimated energy delivered. NS - not significant.

25 had two and seven had three or four replacements, giving a total of 103 IPGs. Since our research question focused on the effect of consecutive IPG replacements, we reassigned the IPG number with the first IPG with adequate information on stimulation parameters being the first IPG. There were no differences in patient gender, age, or disease duration as a function of IPG model or number of IPG replacements per model.

IPG battery longevity for the 1st implanted IPG was 57.6 months for Kinetra[®] and 40.1 months for Activa-PC[®] and it dropped by 10.6 months for Kinetra[®] and 6.0 months for Activa-PC[®] with each subsequent IPG replacement, with significant main effects for IPG model ($p < 10^{-4}$) and for number of previous IPG replacement operations ($p < 10^{-5}$), see Table 1. On including TEED as a covariate, the significance of the IPG model effect increased to $p < 10^{-9}$ and decreased for number of IPG replacements: $p < 0.05$. The effect of TEED on IPG longevity was highly significant: $p < 10^{-13}$.

On taking into account TEED, corrected battery longevity (longevity_c) for the 1st implanted IPG was 51.3 months for Kinetra[®] and 35.6 months for Activa-PC[®] and dropped by 5.9 months for Kinetra[®] and 2.8 months for Activa-PC[®] with significant main effects for IPG model ($p < 10^{-6}$) and for number of previous IPG replacement operations ($p < 10^{-3}$), see Fig. 1.

Stimulation mode was exclusively single monopolar for 38 IPGs and exclusively double monopolar for 24 IPGs (out of 103). By electrodes, 93 were single monopolar, 60 were double monopolar,

9 bipolar and 44 were variable (i.e., differed at the two time points). No electrodes were on interleaving stimulation. There was no difference between Kinetra[®] and Activa-PC[®] (Chi square, $p > 0.05$) regarding stimulation mode.

On comparing the battery longevity_c for patients that underwent Kinetra[®] to Kinetra[®] versus Kinetra[®] to Activa-PC[®] replacements, the former showed less of a drop in longevity, see Fig. 2A. However, in patients that underwent Kinetra[®] to Kinetra[®] to Activa-PC[®] replacements ($n = 6$) there was no significant change, see Fig. 2B.

Discussion

Our two main findings are: (1) IPG longevity_c is longer for Kinetra[®] than for Activa-PC[®] ($p < 10^{-6}$) and (2) IPG longevity_c drops with each subsequent IPG replacement ($p < 10^{-3}$). These two points support previous studies, however we are the first to attempt to correct for changes in DBS parameters (TEED).

With respect to IPG models, both Helmers et al. [22] and Niemann et al. [23] found that longevity was higher for Kinetra[®] than Activa-PC[®] but the differences in TEED are inconsistent between studies (Table 2). Unlike previous papers, we focused solely on PD patients with bilateral subthalamic DBS, without including other movement disorders or brain targets, thus reducing any confounds relating to habituation (greater for thalamic DBS) and different electrode-tissue properties.

Regarding repeated replacements, Niemann et al. [22] found that TEED was correlated with the number of previous replacements and thus proposed that increased TEED may explain reduced battery longevity with consecutive replacements [23]. Based on published data, the relationship between stimulation parameters, different IPG models and battery longevity is less clear. We added insight on these issues by showing that the effect of repeated replacements reducing battery longevity still exists even after correcting for TEED and that the reduction in battery longevity in Activa-PC[®] versus Kinetra[®] is also independent of TEED.

We propose two possible explanations for this finding. Firstly there may be fundamental differences in the battery technologies resulting in energy efficiency with Activa-PC[®] IPG. Secondly a more simple explanation may be that the battery capacity is different which may be related to the markedly decreased dimensions of the Activa-PC[®] IPG.

With respect to the model effect and whether there was a previous Kinetra[®] or not in the case of Activa-PC[®], which requires the use of a pocket adapter, Niemann et al. [23] suggest that this may relate to fluid entering the system and increasing impedance which in turn requires increased stimulation parameters and TEED. However we did not see any increase in TEED in Activa-PC[®] IPGs

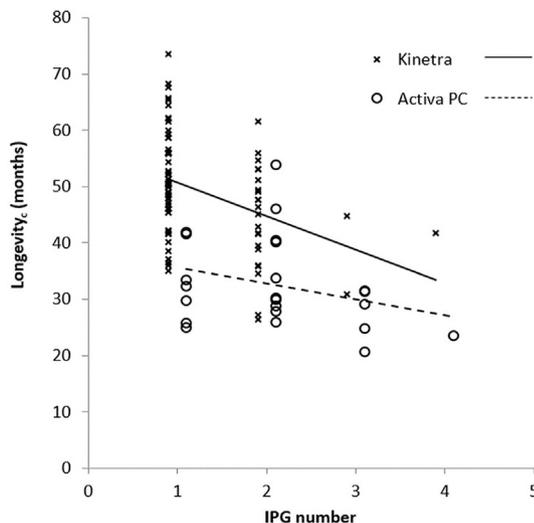


Fig. 1. Corrected longevity as a function of number of IPG replacements for Activa-PC[®] versus Kinetra[®]. The equation for the linear fit for Activa PC is: $y = -2.82x + 38.5$, and for Kinetra is: $y = -5.92x + 56.6$. Abbreviations: Longevity_c: battery longevity corrected for total estimated energy delivered (TEED).

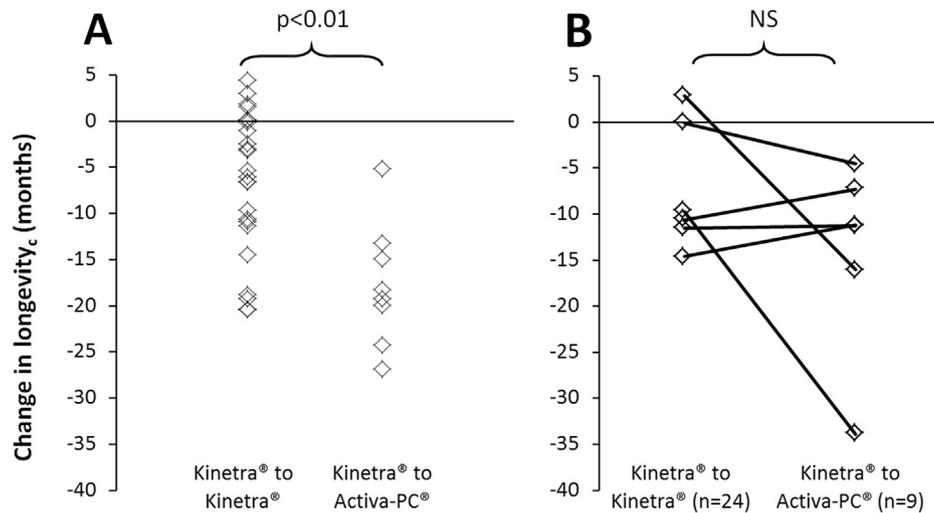


Fig. 2. Change in longevity index in consecutive IPGs. **A:** On comparing the longevity index in patients that underwent Kinetra[®] to Kinetra[®] versus Kinetra[®] to Activa-PC[®] replacements those that were replaced with a further Kinetra[®] showed less of a drop in longevity (corrected for TEED). **B:** In patients that underwent Kinetra[®] to Kinetra[®] to Activa[®] replacements (n = 6) there was no significant trend.

Table 2
IPG Replacements and Battery Longevity: Comparison between our findings and recent literature.

Paper	Current	Niemann et al.	Helmers et al.
Number of centers	1	1	2
Number of patients (all)	62	47	143
Number of PD STN patients	62	18	NR ^a
Number of Kinetra [®] IPGs	80	16	92
Number of Activa-PC [®] IPGs	23	31	51
Stimulation and battery characteristics			
Replacements per patient ^b	1.67 ± 0.76	1.63 ± 0.90	1.00
Therapy impedance	NR	NR	NR
Kinetra [®] TEED (μJ)	265 ± 161	110 ± 54	220 ± 122 ^c
Activa-PC [®] TEED (μJ)	291 ± 138	126 ± 62	145 ± 73
Kinetra [®] longevity (months)	53.8 ± 15.4	81.2 ± 23.6	65.3 ± 2.4
Activa-PC [®] longevity (months)	34.1 ± 11.4	42.6 ± 13.6	53.3 ± 2.0
Findings			
TEED increases with consecutive IPG replacements	p < 10 ⁻⁶	p < 0.001 ^d	NR
Battery longevity reduces with consecutive IPG replacements	p < 10 ⁻⁵ ^e	p < 0.001 ^f	NR
Battery longevity reduces with increasing TEED	p < 10 ⁻¹³ ^f	p < 0.001 ^f	NR

Abbreviations: PD – Parkinson's disease. STN - subthalamic nucleus. IPG - implantable pulse generator. TEED – total estimated energy delivered. NR – not reported.

^a All PD patients, mostly STN electrodes.

^b Mean ± standard deviation.

^c The data was originally presented as mW*Ω, which is equivalent to μJ if we assume an impedance of 1000Ω.

^d LMM with TEED as a covariate: p < 10⁻¹³.

^e This relationship was preserved even after controlling for TEED, p < 10⁻³.

^f Spearman's rank correlation.

that replaced Kinetra[®] IPGs versus Kinetra[®] IPGs that replaced Kinetra[®] IPGs, see Appendix.

Our study has some limitations. The data were retrospective, the distribution of IPG models was not balanced and two important parameters that were not routinely recorded were missing: therapy impedances and battery voltage at IPG replacement. We note that although we routinely measure impedances, until recently we did not record the impedance values in the electronic health records unless they were out of range. Treatment parameters (including pulse width, frequency, voltage and active contacts), however, were reliably documented in the electronic health records. Thus, we estimated the impedance for TEED calculation as 1000 Ω. Of note, in a recent report, although there was a statistically significant downward drift of impedance in STN electrodes, the drop was small

(~90%) and remained stable after 2 years [28]. However, impedance changes post IPG replacement may still provide an explanation to our findings.

Impedance has implications on stimulation intensity, clinical response and battery longevity and has been shown to decrease over time [7,29], potentially explaining at least in part, the reduction in battery longevity as a function of number of previous battery replacement operations.

Another limitation is that in our cohort the distribution of IPG models was not balanced, see Table 1.

DBS has become a mainstay treatment of PD and has been shown to be effective and cost-effective even in the early stages of motor complications [7], and life expectancy with DBS has become decades. Issues relating to battery longevity should be considered

before implantation surgery and replacements, in the choice of IPG model as well as throughout the follow up of a DBS patient—the choice of electrode configuration and stimulation parameters. Clinicians need reliable user-friendly tools built-in the IPG programmer for battery life estimation, to encourage battery-efficient programming.

The poor longevity of the newer IPGs makes rechargeable IPGs a more attractive option for PD. While rechargeable battery technology is now available, it is usually reserved for young patients and patients with dystonia, who need prolonged DBS treatment (often decades) and higher TEED [10,30,31]. There is now increasing interest in treating PD with “non-conventional” DBS parameters involving either altered waveforms [32] or altered frequency [33–35] and with new electrode designs with more contacts, independent current sources and additional functions such as directional steering and sensing capabilities [36,37]. All these developments are likely to have an effect on battery drain. However, currently, recharging involves a significant burden for patients and may not be appropriate for the elderly or people less technologically adept [38,39]. Specifically, in the case of patients with PD, apathy, depression, dementia and punding, recharging may be erratic, inefficient or obsessive, increasing the risk of battery failures. Currently, no consensus exists regarding which patients with PD should be offered rechargeable IPGs [40,41]. There is an urgent need to improve the comfort and user-friendliness of this technology.

Conflicts of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2019.02.008>.

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