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Depleting implanted pulse generator (IPG) battery voltage is associated with worsening clinical symptoms in movement disorder patients receiving Deep brain stimulation (DBS)

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Deep brain stimulation (DBS) results in superior motor symptom control compared to medical treatment alone in properly selected patients with essential tremor (ET), dystonia (DYT), and Parkinson's Disease (PD) [1]. Over time, the battery life of a DBS system's implantable pulse generator (IPG) becomes drained, necessitating replacement [2]. Worsening of motor symptoms accompanying depleted IPG battery life has been reported with earlier Medtronic Kinetra and Soletra models of IPGs [2,3]. However, current generation Activa SC and PC models, which have been designed with Elective Replacement Indicators (ERI) to warn patients of impending IPG battery failure or End-of-Service (EOS), have received less scrutiny.

We performed a retrospective chart review of patients with an implanted DBS system followed in the DBS Program at the University of Alberta who underwent IPG replacement (Activa PC or SC replacements only) between January 1, 2016 and July 31, 2018. Of these patients, we identified those with documented subjective worsening of symptoms attributed to IPG depletion based on clinic notes, and recorded the nature of worsening symptoms, presence or absence of ERI activation, residual battery voltage at time of IPG replacement, and patient-reported symptom response within 3 months following IPG replacement. Patients undergoing IPG replacement for infection ($n = 2$) were excluded, and no patients had undergone medication changes accounting for symptomatic worsening.

A total of 35 instances of IPG replacement in 32 patients (17 PD, 11 DYT, 4 ET) were identified during the study period (Fig. 1). Residual IPG voltage was lower at the clinic visit when the decision was made to replace the IPG compared to the visit immediately prior (mean prior voltage 2.81 ± 0.059 V versus mean voltage at decision-to-replace 2.61 ± 0.16 V, $P < .001$ using paired *t*-test). 12/18 (67%) instances of IPG replacement in PD, 8/13 (73%) instances in DYT, and 4/4 (100%) instances in ET were associated with patient-reported worsening of symptoms at the last clinic visit prior to IPG replacement (overall 24/34 = 71%). Increased fall frequency was the most common symptom in PD, worsening dystonic posturing in DYT, and increased tremor severity in ET. Of instances associated with worsening symptoms, 7/12 (58%) PD, 7/8 (87.5%) DYT, and 1/4 (25%) ET instances had documented worsening of symptoms even prior to ERI threshold (2.6 V). Symptom worsening occurred within 6.0 months following the last reportedly normal timepoint.

All patients undergoing IPG replacement for PD and ET with worsening symptoms before ERI reported subjective improvement following IPG replacement. Subjective symptomatic improvement was observed in 6 out of 7 (85.7%) pre-ERI replacements in DYT. The average residual IPG voltage overall in this subgroup of patients was 2.71 ± 0.04 V (2.73 ± 0.05 V for PD, 2.75 V in ET, and 2.69 +/0 0.02 V in DYT), well above the manufacturer-recommended 2.60 V ERI threshold. That the symptoms of most of these patients improved following IPG replacement suggests not only that low IPG voltage was a proximate cause, but also that ERI indicators on current-generation models may be too permissive, especially for patients with Parkinson's disease or dystonia, where responses to changes in stimulation may take time to manifest.

In contrast, 5/12 (42%) of symptomatic PD and 3/4 (75%) of ET IPG replacements occurred at or after ERI. Symptoms improved in 7 of these patients (5 PD and 2 ET). Only one patient out of 8 (12.5%) symptomatic dystonia patients had IPG replaced at or after ERI, but symptoms did not improve following replacement. Average IPG voltage prior to replacement in this subgroup was 2.50 ± 0.10 V.

UPDRS-III scores in the OFF-medication ON-stimulation condition were available for a subset of PD patients with symptomatic worsening who underwent IPG replacement. Median UPDRS-III score increased significantly (i.e., worsened) between the timepoint prior to symptom worsening, and at the timepoint of reported symptom worsening, across 11 PD patients in whom these data were available (16.0 at the penultimate time point versus 21.0 at the time of reported symptom worsening, $P = .001$, Wilcoxon signed-rank test). Median UPDRS-III score did not show statistically significant change between the timepoint of reported symptom worsening and 1-month post-IPG replacement, across 12 patients in whom these data were available (19.5 versus 19.0, $P > .05$). However, median UPDRS-III score in the OFF-medication ON-stimulation condition showed a non-significant trend toward improvement between the 1-month and 6-months post-IPG replacement for 11 patients in whom these data were available (19.0 vs. 16.0), suggesting a durable motor improvement following IPG replacement despite expected progression of the disease.

Six PD (3 before ERI, 3 at or after ERI), 7 dystonia (5 before ERI, 2 at or after ERI), and 2 ET (both at or after ERI) instances had reprogramming trials prior to replacement, but none of the parameters were changed after IPG replacement compared to immediately before IPG replacement. Furthermore, there was no statistically significant difference in therapy impedance prior to and after IPG replacement (1113.09 ± 378.73 Ω before replacement vs. 938.59 ± 626.26 Ω following replacement, $p > .05$).

Literature addressing low IPG battery voltage and replacement reports similar findings to ours in older IPG generations. Fakhar et al. (2013) looked at 320 patients undergoing DBS battery replacement over 10 years and found that 38 out of 75 patients with available clinical data who underwent IPG replacement experienced symptom improvement following Kinetra/Soletra IPG replacement, while the remaining 37 had symptom stability or worsening [2]. This mirrors our results, though our sample size was comparatively

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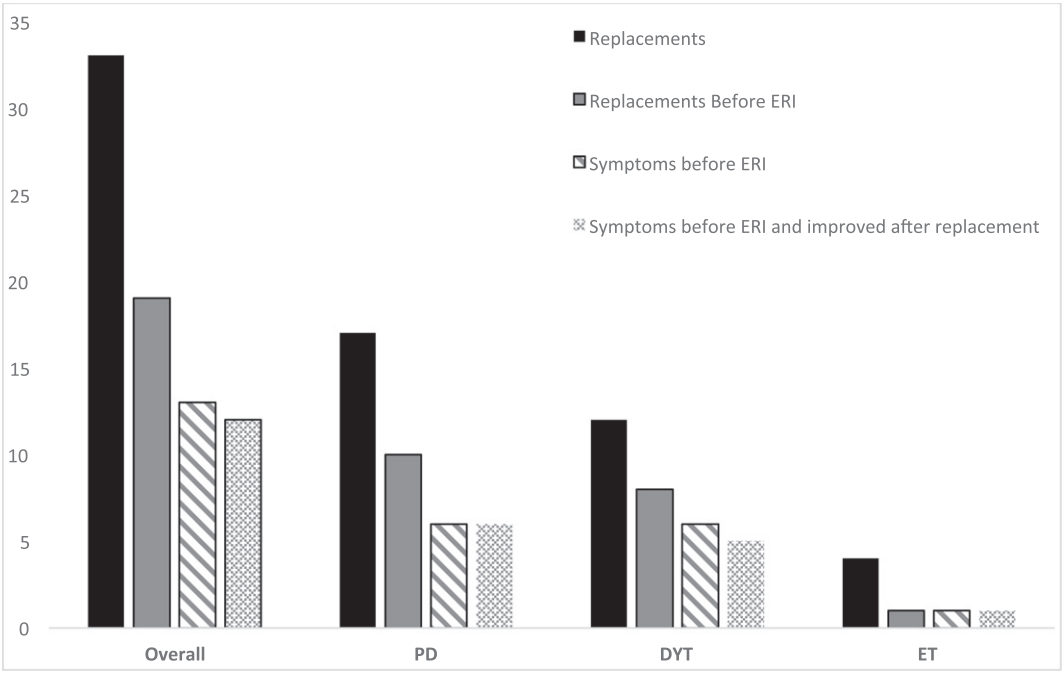

Fig. 1. Bar graph demonstrating number of implantable pulse generator (IPG) replacements per diagnosis (black), number of replacements before Elective Replacement Indicator (ERI) activation (gray), number of instances of IPG replacement prior to ERI that experienced worsening symptoms (diagonal lines), and number of instances of IPG replacement prior to ERI associated with symptom improvement following IPG replacement (dots).

smaller. Mehanna et al. (2014) looked at 55 Soletra IPG replacements and found that only 25.5% of patients were clinically well-controlled prior to IPG replacement [3]. Another study by Vora et al. looked at rebound symptoms in 6 DBS patients with obsessive-compulsive disorder who experienced IPG depletion and found that 5 of them (83.33%) returned to baseline Yale-Brown Obsessive Compulsive Scale scores following IPG replacement [4]. All these studies investigated the older Activa Kinetra and Soletra models; to our knowledge, the current Activa PC and SC models have not been investigated in a similar fashion to date.

Despite our small sample size, the possibility of disease progression (although a 6.0-month time period is hardly sufficient for PD, dystonia, or ET to progress), and the possibility of nocebo and placebo effects (where patients report symptomatic worsening when told their IPGs require replacement or, conversely, symptomatic improvement following IPG replacement) [5], we have demonstrated that close monitoring of IPG battery life continues to be a sensible practice. The placebo and nocebo effects were to some extent mitigated by routine standard of care at our clinic which involves interrogating the IPG only after a history is taken from the patient. Our data would suggest that ERI thresholds may need to be revised for the current Activa generation of IPGs. Importantly, our findings emphasize the importance of making the decision to proceed with IPG replacement on an individualized basis, informed by each patient's clinical context, even if IPG battery life has not yet reached ERI. In the same vein, while IPGs may provide service for several months following ERI alerts [3], consideration must be given to programming retrials to lessen the medical expenses of potentially unnecessary IPG replacement. Future studies should address this concern with larger sample sizes and objective clinical rating scales, further taking into account whether programming retrials and troubleshooting have been completed.

Declaration of competing interest

Moath Hamed MD declares no competing financial disclosures or conflicts of interest.

Fang Ba MD PhD FRCPC declares no competing financial disclosures or conflicts of interest.

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