ARTIGO ORIGINAL/ORIGINAL ARTICLE

Hybrid Deep Brain Stimulation for Parkinson's Disease and Dystonia Improves Side Effects, Maintaining Clinical Benefit

Estimulação Cerebral Profunda Híbrida na Doença de Parkinson e Distonia Melhora Efeitos Laterais, Mantendo o Benefício

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Abstract

Introduction: Deep brain stimulation (DBS) in movement disorders does not always achieve optimal symptomatic control. Most common issues involve suboptimal electrode positioning and target stimulation and troublesome side effects limiting the therapeutic window. Recently approved implantable pulse generators (IPG) allow for pulse widths lower than 60 µs, increasing the therapeutic window, and current steering. These new constant-current IPG (CC-IPG), in addition to these characteristics, have rechargeable, thus longer duration, batteries. This work aims to describe a tertiary center's experience with replacing a constant-voltage stimulation non-rechargeable implantable pulse generator (CV-IPG), at the end of its battery's lifespan, with a CC-IPG, with more options in pulse duration changes and multiple-source current steering.

Methods: A retrospective review of the clinical records of patients submitted to DBS who had their CV-IPG replaced with CC-IPG was performed, documenting reason for preference, stimulation parameters, clinical benefit pre and post-replacement and side effects.

Results: Six patients who fulfilled the criteria were identified, four with Parkinson's disease (PD) and two with dystonia. The reasons for preference were: stimulation side effects (2), suboptimal benefit (1), long battery duration (3). Side effects were improved by using a 30 µs pulse in two patients. Current steering allowed the shortening of OFF periods in 1 PD patient. One patient with dystonia had initial decrease in clinical benefit but recovered after amplitude correction according to impedance. The other two patients remained stable post-replacement.

Conclusion: Replacement of CV-IPG with CC-IPG proved feasible and safe, with non-inferior clinical benefit, additionally providing pulse lowering and current steering strategies for solving suboptimal results with DBS.

Resumo

Introdução: O tratamento de doenças do movimento com estimulação cerebral profunda (DBS) nem sempre alcança um controlo sintomático ótimo. Os problemas mais comuns incluem posicionamento dos elétrodos ou estimulação do alvo sub-

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-ótimos e efeitos laterais incomodativos que limitam a janela terapêutica. Geradores de pulso implantados (IPG) recentemente aprovados permitem intervalos de pulso inferiores a 60 µs, aumentando a janela terapêutica, e direcionamento da corrente através de *multiple source current steering*. Estes novos IPG de corrente constante (CC-IPG), para além destas características, têm baterias recarregáveis e com duração mais longa. Este trabalho procurar demonstrar a viabilidade, segurança e eficácia de substituir um IPG não-recarregável de voltagem constante (CV-IPG), em fim de vida da bateria, por um CC-IPG, com mais opções de alteração da duração do pulso e direcionamento de corrente.

Métodos: Foi efetuada uma revisão retrospetiva dos processos clínicos dos doentes tratados com DBS que tiveram o seu CV-IPG substituído por um CC-IPG, documentando a razão para a preferência, parâmetros de estimulação, benefício clínico pré e pós-substituição e efeitos laterais.

Resultados: Seis doentes que cumpriam os critérios foram identificados, quatro com doença de Parkinson (PD) e dois com distonia. As razões para a preferência foram: efeitos laterais da estimulação (2), benefício sub-ótimo (1), duração da bateria mais longa (3). Efeitos laterais melhoraram usando um pulso de 30 µs em dois doentes. Direcionamento da corrente permitiu o encurtamento dos períodos em OFF de um doente com PD. Um doente com distonia teve diminuição inicial do benefício clínico, mas recuperou após correção da amplitude de acordo com a impedância. Os outros dois doentes permaneceram estáveis pós-substituição.

Conclusão: A substituição de um CV-IPG por um CC-IPG mostrou-se viável e segura, com benefício clínico não inferior, dando estratégias adicionais de diminuição do pulso e direcionamento de corrente para resolver resultados sub-ótimos do tratamento com DBS.

Introduction

Deep brain stimulation (DBS) is a proven effective therapy for the treatment of patients with movement disorders, most used in Parkinson's disease (PD) and dystonia. Possible stimulation targets include the subthalamic nucleus (STN) for both PD and dystonia, the ventral intermediate nucleus (Vim) of the thalamus for tremor and the internal globus pallidus (GPi) for PD and dystonia. Implantable pulse generators (IPG) generating constant-voltage stimulation have been the first to become available, and the mainstay in this type of therapy.[1,2]

Several issues can be encountered when managing movement disorder patients treated with DBS. Amongst the most common are lack of efficacy due to suboptimal electrode positioning and troublesome side effects that limit the therapeutic window. These side effects, depending on what structures are being inadvertently stimulated, take many forms, including dysarthria, dysphonia, dysphagia, involuntary limb contraction, gait impairment, dyskinesia, ataxia and paraesthesia, amongst others.[3]

Newly introduced IPG, which use constant-current stimulation in opposition to constant-voltage stimulation, have been shown to be effective in the treatment of PD.[4,5] Switching from constant-voltage to constant-current stimulation (using the same device) in stable chronically STN-stimulated PD patients has also been safely performed.[6] Constant-current stimulation allows for an automatic adaptation of stimulation intensity to varying impedance values, possibly minimizing loss of efficacy in the long-term. Additionally, the new IPG have enabled new strategies to deal with DBS side effects or efficacy issues through pulse width lowering, proven to increase the therapeutic window, and multiple-source current steering.[5,7–13] Multiple-source current steering is a technology where each of the four contacts in the electrode has its own current source – each contact can thus be

individually activated and programmed and generate its own stimulation field, allowing for more complex stimulation field shaping with optimization of volume of activated tissue.[14] The new constant-current rechargeable IPG present additional advantage in the form of a longer durability, currently estimated at 25 years.

The aim of this study was thus to describe a tertiary centre's experience with the replacement an Activa PC® IPG (Medtronic, Minneapolis, MN, USA), a constant-voltage stimulation device (CV-IPG), at the end of its battery's lifespan, with a Gevia™ IPG (Boston Scientific, Natick, MA, USA), a rechargeable constant-current stimulation device (CC-IPG) with new options in pulse width changes and multiple-source current steering, by describing its feasibility, safety and efficacy in helping solve or ameliorate suboptimal benefit or side effects of DBS.

Material and Methods

Clinical records of movement disorder patients treated with DBS in the Department of Neurology of Centro Hospitalar Universitário do Porto from 2005 to 2021 were retrospectively reviewed. All patients who had had their CV-IPG replaced with a CC-IPG were included. The following aspects were documented: a) reason for the preference for CC-IPG; b) stimulation parameters pre and post-replacement; c) clinical benefit pre and post-replacement, assessed by Part III of the Unified Parkinson's Disease Rating Scale (UPDRS III) for PD patients and clinician's evaluation together with patient's own impression for dystonia patients; d) side effects pre and post-replacement. Evaluating physician was the patient's neurologist who provided routine DBS care and follow-up, and so was not blinded to the parameters. The patients were observed longitudinally in regular outpatient visits, where stimulation parameters were adjusted and clinical evaluation was performed before and after each adjustment to evaluate for clinical benefit and side effects.

Results

Six patients meeting the inclusion criteria were identified. Four patients had PD and two had dystonia. Patients were first assessed by the neurologist 3 to 6 months after the replacement; the most recent clinical evaluation available was also reviewed. **Table 1** summarizes the main reasons for choosing the new IPG, stimulation parameters and clinical benefit. PD patients were evaluated at the condition medication OFF, after at least 12 hours without antiparkinsonian medication, and stimulation ON (OFF MED/ON STIM).

Patient 1. The first patient was a 71-year-old man with 21 years of PD and submitted to STN-DBS at 61 years of age. He had dysarthria and left upper limb contraction, not improved after successive parameter ad-

Table 1. Characteristics, reasons for choice, treatment strategy and clinical benefit of patients who underwent constant-voltage to constant-current stimulation device replacement.

#	Gender	Diagnosis	Target	Age at symptom onset	Age at first DBS	Reason for choice	Stimulation parameters pre-replacement	Strategy	Stimulation parameters post-replacement	Clinical benefit
1	Male	PD	STN	50	61	Side effects	**R** 1- 3.4v/60 µs/130 Hz **L** 6- 3.1v/60 µs/130 Hz	Lower pulse width	**R** 2- 6 mA/30 µs/130 Hz **L** 11- 4.5 mA/60 µs/130 Hz	Same with less side effects
2	Female	PD	STN	25	41	Side effects Patient's age	**R** 2- 1.8v/60 µs/125 Hz 3-1.9v/60 µs/125 Hz **L** 9- 2,2v/60 µs/125 Hz	Lower pulse width	**R** 11- 4.3 mA/30 µs/130 Hz (60%) 12- 4.3 mA/30 µs/130 Hz (40%) **L** 2- 3.2 mA/30 µs/130 Hz	Same with less side effects
3	Male	PD	STN	45	51	Suboptimal benefit Patient's age	**R** 2- 3.2v/60 µs/130 Hz **L** 10- 3.5v/60 µs/130 Hz	Current steering	**R** 2- 4.8 mA/60 µs/130 Hz (30%) 3- 4.8 mA/60 µs/130 Hz (70%) **L** 10- 3.2 mA/60 µs/130 Hz	Improved
4	Male	PD	STN	49	67	Life expectancy Recharge	**R** 1- 2.9v/60 µs/130 Hz **L** 9- 2.4v/60 µs/130 Hz	-	**R** 2- 3.3 mA/60 µs/130 Hz **L** 10- 2.8 mA/60 µs/130 Hz	Same
5	Female	Dystonia	GPi, STN	9	18	Patient's age	**R** 2- 3.2v/60 µs/130 Hz **L** 10- 3.2v/60 µs/130 Hz	-	**R** 3- 3.6 mA/60 µs/130 Hz **L** 11- 3.6 mA/60 µs/130 Hz	Same
6	Male	Dystonia	Vim, GPi	6	31	Patient's age	**Vim** 2-4.1v/60 µs/130 Hz **GPi** 5- 4.4v/60 µs/130 Hz	-	**Vim** 3- 4.5 mA/60 µs/130 Hz **GPi** 10- 5.7 mA/60 µs/130 Hz	Same

GPi: internal globus pallidus. L: left lead. PD: Parkinson's disease. R: right lead. STN: subthalamic nucleus. Vim: ventral intermediate nucleus of the thalamus.

justments. Before IPG switch he had the following stimulation parameters: right lead (RL) 1- 3.4v/60 μs/130 Hz, left lead (LL) 6- 3.1v/60 μs/130 Hz. He scored 27 on UPDRS III (OFF MED/ON STIM). After IPG replacement, pulse width was lowered on the right lead (new stimulation parameters: RL 2- 6 mA/30 μs/130 Hz, LL 11- 4.5 mA/60 μs/130 Hz), with a clear improvement of dysarthria and a diminished frequency of left upper limb contraction, while maintaining clinical benefit (UPDRS III score 27, OFF MED/ON STIM, post-replacement). In the most recent clinical evaluation, 3 years and 6 months after IPG replacement, his axial symptoms, non-responsive to DBS, had progressed and are now the main source of disability, although benefit in stimulation side effects is maintained.

Patient 2. A 47-year-old woman with PD since the age of 25 who was submitted to STN-DBS at 41 years of age. She complained of side effects, namely dysarthria, cough and dysphagia, which persisted despite multiple programming strategies, including current steering by interleaving. Pre-replacement stimulation parameters were: RL 2- 1.8v/60 μs/125 Hz 3- 1.9v/60 μs/125 Hz, LL 9- 2.2v/60 μs/125 Hz. She scored 16 on UPDRS III (OFF MED/ON STIM). Her young age was a factor in switching to a longer duration device. Post-replacement, to improve side effects, stimulation parameters were adjusted: current steering was optimized in the RL and the pulse was lowered to 30 μs bilaterally. Stimulation parameters after replacement were as follows: RL 11- 4.3 mA/30 μs/130 Hz (60%) 12- 4.3 mA/30 μs/130 Hz (40%), LL 2- 3.2 mA/30 μs/130 Hz. Complete resolution of cough and dysphagia and marked improvement in dysarthria were achieved. Clinical benefit was maintained, with an UPDRS III score of 16 (OFF MED/ON STIM). At last evaluation, 3 years and 6 months after IPG replacement, clinical benefit without troublesome side effects is maintained.

Patient 3. The third patient was a 59-year-old male who had PD for 14 years and had been under STN-DBS for the past 8 years. He maintained motor fluctuations with significant evening wearing-off that impaired his quality of life. He scored 18 on UPDRS III (OFF MED/ ON STIM), and was on the following stimulation parameters: RL 2- 3.2v/60 μs/130 Hz, LL 10- 3.5v/60 μs/130 Hz. Post-replacement, current steering was applied on the right electrode, with the parameters: RL 2- 4.8 mA/60 μs/130 Hz (30%) 3- 4.8 mA/60 μs/130 Hz (70%), L 10- 3.2 mA/60 μs/130 Hz. The patient experienced complete resolution of wearing-off, scoring 16 on re-evaluation by UPDRS III (OFF MED/ON STIM). At most recent evaluation, 3 years and 6 months after IPG replacement, benefit in motor fluctuations was maintained and the UPDRS III (OFF MED/ ON STIM) was 15.

Patient 4. This was a 73-year-old male patient who had PD for 24 years and was started on STN-DBS 6 years before IPG replacement. He was on the following stimulation parameters: RL 1- 2.9v/60 μs/130 Hz, LL 9- 2.4v/60 μs/130 Hz, with a good clinical benefit and no reported side effects, scoring 21 on UPDRS III (OFF MED/ON STIM). The choice of a CC-IPG was due to its longer durability. The post-replacement parameters were as follows: RL 2- 3.3 mA/60 μs/130 Hz, LL 10- 2.8 mA/60 μs/130 Hz. He maintained clinical benefit, with a UPDRS III score of 21 (OFF MED/ON STIM), and developed no side effects. At most recent evaluation, with 8 years of DBS and 3 years and 6 months after IPG switch, he had developed progressive DBS-resistant axial symptoms, namely postural instability and start-hesitation of gait, scoring 32 on the UPDRS III (OFF MED/ON STIM).

Patient 5. The fifth patient was a 36-year-old woman with DYT1-related generalized dystonia since she was 9 years old, initially submitted to GPi-DBS with great clinical benefit and, 14 years later, to STN-DBS due to progression of lower limb dystonia with feet inversion and hyperextension and severe gait impairment. With STN-DBS, lower limb dystonia markedly improved, gait was again possible without assistance and upper limb dystonia remained well controlled under the following stimulation parameters: RL 2- 3.2v/60 μs/130 Hz, LL 10- 3.2v/60 μs/130 Hz. Because of age and longer durability, a CC-IPG was preferred. Post-replacement, at a 3-month follow-up, she presented with worsening of her dystonia. Her stimulation parameters at the time were: RL 3- 3.2 mA/60 μs/130 Hz, LL 11- 3.2 mA/60 μs/130 Hz. It was noted that selected amplitude parameter had not been adjusted for the pre-replacement impedance. After parameter adjustment (RL 3- 3.6 mA/60 μs/130 Hz, LL 11- 3.6 mA/60 μs/130 Hz) the patient quickly regained the same benefit she had with the previous IPG, and no further complications were reported. She maintains clinical benefit at most recent evaluation, 3 years and 6 months after replacement.

Patient 6. A 47-year-old man with hemidystonia secondary to traumatic brain injury sustained at 6 years

of age was submitted to DBS targeting the left Vim and the GPi at age 31, maintaining good clinical benefit over the next 16 years, with no side effects. Replacement with a CC-IPG device was preferred because of age and longer durability. Pre-replacement, he had the following stimulation parameters: Channel 1 (Vim) 2- 4.1v/60 μs/130 Hz, Channel 2 (GPi) 5- 4.4v/60 μs/130 Hz. Post-replacement, the parameters were adjusted to the following: Channel 1 (Vim) 3- 4.5 mA/60 μs/130 Hz, Channel 2 (GPi) 10- 5.7 mA/60 μs/130 Hz. He maintained the same clinical benefit with no side effects in the immediate post-replacement period and at most recent clinical visit, 3 years and 6 months after IPG replacement.

Discussion

The new CC-IPG was found to be non-inferior to the previous CV-IPG in all the cases reviewed. Clinical benefit was consistently maintained, independently of whether they presented with suboptimal benefit or stimulation side effects previous to the switch (patients 1 to 3) or not (patients 4 to 6). This goes in line with previous reports describing constant-current stimulation as non-inferior to constant-voltage stimulation.[4,5,15]

In one patient who presented with suboptimal clinical benefit (patient 3), current steering was applied after replacement. This allowed for the distribution of the current between the lead which was already being used previously and the lead immediately above it, and a clinical benefit was noted. It is thought that the multiple-source current steering permitted by CC-IPG, with its percentage-guided approach and ability to select multiple contacts for activation, is able to provide more precise stimulation fields and steer the current more accurately towards the targeted areas of interest.[11–13] Some trials have already demonstrated motor and quality of life benefit in patients with this approach.[5] It is worth noting that interleaving had not been tried previous to replacement, and could have afforded some benefit. However, previous generation single-source devices, which offer interleaving, distribute current in a less predictable manner, being less intuitive in their fractioning and giving less control to the programmer.[13] Additionally, interleaving increases battery drain and consequently lowers IPG duration. Comparative studies between the two are still lacking.

In the two patients with stimulation side effects (patients 1 and 2), a clear benefit in side effect control was achieved with the possibility of pulse width lowering afforded by the new IPG. Recent studies have demonstrated the existence of an inverse relation between pulse width and the amplitude thresholds for clinical benefit and side effects.[7–10] Lowering pulse width to values below 60 μs has been shown to expand the therapeutic window for a given electrode, by increasing the amplitude limit above which side effects appear. Although the amplitude needed for clinical benefit is also increased, it does so in a lesser degree than the side effects threshold, effectively expanding the range of side effect-free effective amplitudes.[7–10] This is thought to be a consequence of selective stimulation of the smaller axons of the STN, while sparing the comparatively longer and myelinated axonal fibers of the pyramidal tract neurons due to excitability differences.[7] These two patients underwent pulse width adjustment from 60 μs to 30 μs, as has been done in most previous articles dealing with lower pulse width. The current amplitude had to be increased accordingly to achieve the same clinical benefit as before, but diminished side effects were noted for the same clinical benefit, with some of them resolving altogether. In patient 1, since the main side effect was unilateral (left upper limb contraction), only the pulse on the right lead was lowered, with acceptable side effect control. In patient 2, since the side effects were mostly axial (dysarthria, dysphagia, coughing), pulse on both leads was lowered, and the only side effect not totally resolved was dysarthria.

A post-replacement temporary loss in clinical benefit was noted in patient 5. This was ultimately attributed to an undervaluing of impedance values. Impedance is the resistance to electrical delivery to the brain, translating the characteristics of the electrode and of the electrode-brain interface.[12] The amount of stimulation being delivered, i.e., the current intensity, is directly correlated with the voltage, and inversely correlated with the impedance.[12] As such, when changing from a constant-voltage to constant-current device, the clinician needs to determine the new intensity parameters by converting from the previous voltage settings, considering the electrode impedance. Failing to do so might lead to loss of benefit or appearance of side effects, as occurred with this patient.

There are previous studies showing the safety and feasibility of changing from a constant-voltage to constant-current setting maintaining the same device in

chronically DBS-treated PD.[6] Two other reports have also explored the feasibility and clinical benefit of a new constant-current IPG connected to the patient's existing electrodes (hybrid stimulation), previously with a constant-voltage device, in PD and dystonia.[16,17] This report expands on this knowledge by documenting examples of clinical utility of other features included on these IPG, such as pulse width customization and current steering, for PD and dystonia. A previous work reports on two patients with essential tremor treated with Vim-DBS who maintained important side effects and underwent the same replacement (constant-voltage non-rechargeable IPG to constant-current rechargeable IPG), using the possibility of lowering the pulse to increase the therapeutic window, with a marked clinical benefit.[18] Their work found it feasible and safe to connect the new device with the previous one's electrodes, as in this series.

A limitation of these hybrid systems, due to combining hardware of different manufacturers, is the restriction on performing magnetic resonance imaging on these patients – research for a solution is ongoing. Also, rechargeable IPG present disadvantages: patients or caregivers need to learn how to use the recharging device and must check battery and recharge regularly, possibly interfering with patients' daily lives; there is the possibility of forgetting to charge the device, leading to IPG battery depletion, with possibly dire consequences; the device itself is also more expensive than a non-rechargeable IPG.

This study presents several limitations, namely a small sample size and its retrospective and descriptive design, restricting its power to draw generalized conclusions. Ultimately, these new strategies for symptom and side effect control, proven effective, can contribute to a better treatment of neurological patients with DBS, optimizing a technology that is complex but clinically rewarding.

Conclusion

In conclusion, replacement of a constant-voltage stimulation device with a rechargeable constant-current stimulation device with new options in pulse width changes and multiple-source current did not pose any technical issues, clinical benefit was found to be non-inferior to previous IPG, and in some cases improved efficacy and side effects. It is important to consider pre-replacement impedance when switching from constant-voltage to constant-current stimulation. Pulse width lowering and multiple-source current steering contributed to minimize common DBS problems. Longer duration of the new IPG is an important advantage, avoiding successive replacements and lowering associated surgical risks, such as infection. ■

Contributorship Statement / Declaração de Contribuição

DC: acquisition of the data, interpretation of the data, writing the manuscript.

MC: acquisition of the data, interpretation of the data, manuscript review and final approval.

NVC, JD, CS, EPC, LB and AV: acquisition of the data, manuscript review and final approval.

AM: design of the work, acquisition of the data, interpretation of the data, manuscript review and final approval.

Responsabilidades Éticas

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Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

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