ORIGINAL ARTICLE

Switching from constant voltage to constant current in deep brain stimulation: a multicenter experience of mixed implants for movement disorders

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Keywords: constant-current stimulation, constant-voltage stimulation, deep brain stimulation, mixed implants

Received 15 February 2015
Accepted 3 August 2015

European Journal of Neurology 2016, **23:** 190–195

doi:10.1111/ene.12835

Background and purpose: For many years deep brain stimulation (DBS) devices relied only on voltage-controlled stimulation (CV), but recently current-controlled devices have been developed and approved for new implants as well as for replacement of CV devices after battery drain. Constant-current (CC) stimulation has been demonstrated to be effective in new implanted parkinsonian and dystonic patients, but the effect of switching to CC therapy in patients chronically stimulated with CV implantable pulse generators (IPGs) has not been assessed. This report shows the results of a consecutive retrospective data collection performed at five Italian centers before and after replacement of constant-voltage with constant-current DBS devices, in order to verify the clinical efficacy and safety of this procedure.

Methods: Nineteen patients with Parkinson's disease or dystonic syndrome underwent DBS IPG CV/CC replacement. Clinical features and therapy satisfaction were assessed before surgery, 1 week after and 3 and 6 months after replacement. Programming settings and impedances were recorded before removing the CV device and when the CC IPGs were switched on.

Results: The clinical outcome of CC stimulation was similar to that obtained with CV devices and remained stable at 3 and 6 months of follow-up. Impedance values recorded for CV and CC IPGs were similar. Ninety-five percent of patients and physicians were satisfied with mixed implants. No adverse events occurred after IPG replacement.

Conclusion: Replacing CV with CC IPGs is a safe and effective procedure. Longer follow-up is necessary to better clarify the impact of CC stimulation on clinical outcome after chronic stimulation in CV mode.

Introduction

Deep brain stimulation (DBS) is an established treatment for Parkinson's disease (PD) and dystonia also in long-term follow-up [1–4]. Different types of implantable pulse generators (IPGs) are available for DBS.

1 Voltage-controlled (CV) DBS devices deliver an adjustable voltage across the stimulating electrodes. In these systems the therapeutic current and the volume of tissue activated in CV IPGs may vary due to changes in the impedance of the tissue and the electrode–tissue interface [5–7]. Recent studies show that impedances vary over time and over different time frames [8–13].

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2 Constant-current-controlled (CC) IPGs deliver constant current, automatically accommodating the voltage on the base of impedance variations [5,6,14].

The recent literature underlined the non-inferiority of CC compared to CV stimulation in newly implanted patients [6,8,15], also in long-term follow-up [16]. Potentially, CC IPGs could produce more predictable physiological effects, by preventing changes in the volume of tissue activated.

Constant-current-controlled devices have also been recently approved for replacement of depleted CV IPGs. New IPGs can be connected to previously implanted electrodes and extensions by the same or by a different manufacturer through the use of an adapter. In our series, leads, extensions and CC IPGs were provided by different manufacturers, so such hybrid systems are referred as 'mixed implant'.

No data are available about the possible effect of changing stimulation mode in chronic implanted patients. The purpose of this retrospective, consecutive data collection was to evaluate the safety and effectiveness of CC stimulation in patients with previous long-lasting CV stimulation.

Methods

This is a retrospective real-life analysis of a multicenter data collection performed across five Italian centers, including 19 consecutive patients who underwent DBS IPG replacements from CV to CC. According to our local regulations, analyses of data collected for clinical purposes do not require approval by the ethical committee.

Before replacement, all patients were implanted with Medtronic Kinetra™ or Soletra™ (Medtronic Inc., Minneapolis, MN, USA) IPGs and were chronically stimulated in CV mode. Before complete battery exhaustion, CV IPGs were replaced with CC IPGs (Libra XP™ or Brio™ devices; St Jude Neuromodulation, Plano, TX, USA) by the use of a standard CE-marked adapter (IS-1 Pocket Adapter; St Jude Neuromodulation).

After replacement, the same contacts setting used in the CV mode were activated in CC IPGs. Pulse width and frequency used before replacement were programmed on the new IPG. CC amplitude was calculated using the following formula: CV system tension (V)/CV system impedance (Ω). 'Impedance therapy' values were obtained by Medtronic DBS programmer (N'Vision, Medtronic Inc.,) before replacement. Further adjustments of stimulation settings were carried out, if necessary, based on clinical response.

For each patient the following data were collected.

1 Motor scores were obtained before and 3 and 6 months after the replacement: Unified Parkinson's Disease Rating Scale part III, ON Stim, ON Med, in PD patients, and Burke–Fahn–Marsden Dystonia Rating Scale in dystonic patients. For pre-replacement assessment the motor scores obtained in CV stimulation mode at the last visit performed before battery wasting were considered (time elapsed from this evaluation to replacement ranged from 2 to 6 months). Motor scores assessed immediately before the replacement were not considered in order to avoid a bias related to a worsening of symptoms, which could occur close to the battery depletion in CV mode [7].
2 Semi-structured interviews were given to physicians and patients on the clinical efficacy of CC stimulation, rated on a three-point Clinical Global Impressions (CGI) scale (improvement, no change, worsening) after 1 week and 3 and 6 months from the CC replacement.
3 Patient's feedback about the recharging procedure was noted after 6 months from the CC substitution in six of 19 patients, where rechargeable systems were chosen as replacement.
4 The number of replacements that occurred before the replacement with a CC device was noted.
5 The mean battery duration between each CV replacement, if other replacements occurred before the substitution from CV to CC IPGs, was registered
6 The number of programming sessions necessary to reach the same pre-replacement clinical outcomes after every substitution was noted.
7 Information about the programming settings and therapy impedances of IPGs was obtained before and 1 week and 3 and 6 months after the replacement.
8 Adverse events due to the surgical procedure and side effects related to a mixed implant were recorded.

Continuous data are presented as mean ± SD. For all continuous collected variables, differences before and after replacement were evaluated by means of ANOVA for repeated measures analysis with Bonferroni adjustment for *post hoc* comparisons. All two-tailed P values < 0.05 were considered statistically significant. The STATA ver. 13 (StataCorp, Collage Station, TX, USA) statistical package was used for the analysis.

Results

In this data analysis 13 PD patients and six primary dystonic patients were included. In all PD patients DBS leads were implanted in the subthalamic nucleus,

whilst in dystonic patients the target was the globus pallidus internus.

At 3- and 6-months follow-up, motor scores in the CC mode did not show a significant difference in comparison to the clinical outcomes obtained with CV devices (Table 1).

The main modification in CGI after the CC replacement is reported after 1 week and 3 and 6 months compared with the clinical condition before the changeover in Figs 1 and 2.

When improvement was stated, both neurologists and patients reported amelioration in motor performances; in particular gait and phonation improved in three parkinsonian patients, and amelioration of dysarthria and in motor tasks were observed in four dystonic patients. These results were maintained at 3 and 6 months.

After 6 months, 95% of patients and physicians would again choose a CC replacement, and 95% of patients were satisfied or fully satisfied with the CC replacement.

Three PD patients had never been submitted to IPG change before; the other 16 patients (six dystonic and 10 PD patients) had undergone replacement to CV IPG once ($n = 13$) or twice ($n = 3$). No CV IPGs were rechargeable, whilst 33% (two) of dystonic patients and 31% (four) of parkinsonian patients were implanted with a rechargeable CC IPG. For 100% of patients the rechargeable procedure was acceptable (20%) or comfortable (80%).

Considering the whole population, the mean battery longevity of CV IPGs was 4.3 ± 1.7 years (3.5 ± 2.1 years for six dystonic patients, 4.9 ± 1.3 years for

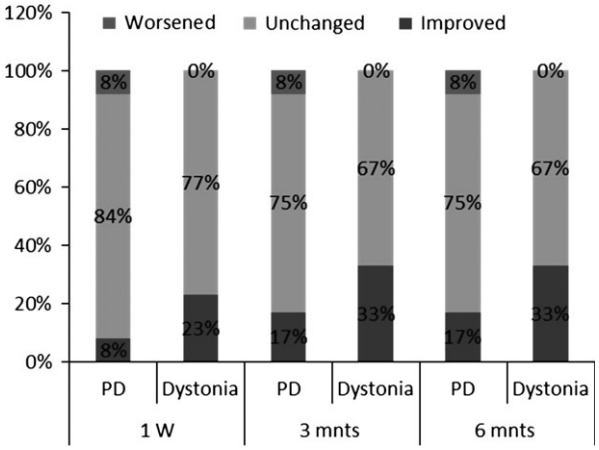

Figure 1 Physician CGI after 1 week and 3 and 6 months from replacement.

Table 1 Motor scores before and 3 and 6 months after replacement

	Pre-replacement	At 3 months follow-up	At 6 months follow-up	Percentage improvement at 3 months	Percentage improvement at 6 months	*P*
UPDRS III						
All PD patients	33.4 ± 13.4	33.5 ± 14.8	32.6 ± 13.6	1.1 ± 6.8	3.2 ± 5.4	NS (0.71)
Patient 1[a]	57	61	57	−7	0	
Patient 2[b]	45	43	43	4	4	
Patient 3[b]	21	17	17	19	19	
Patient 4[b]	14	13	13	7	7	
Patient 5	48	48	47	0	6	
Patient 6	31	31	31	0	0	
Patient 7	21	21	21	0	0	
Patient 8	34	34	33	0	3	
Patient 9	40	40	40	0	0	
Patient 10	24	24	24	0	0	
Patient 11	19	19	19	0	0	
Patient 12	31	31	31	0	0	
Patient 13[a]	48	53	48	−10	0	
BFMDRS						
All dystonic patients	25.3 ± 13.5	23.1 ± 12.8	22.8 ± 12.9	8.4 ± 8.8	9.9 ± 10.4	NS (0.053)
Patient 1[b]	32	26	25.5	19	20	
Patient 2	24	24	24	0	0	
Patient 3[b]	19	17.5	17	8	10	
Patient 4	8.5	8.5	8.5	0	0	
Patient 5[b]	20.5	16.5	15.5	19	24	
Patient 6[b]	48	46	46	4	4	

UPDRS III, Unified Parkinson's Disease Rating Scale part III; BFMDRS, Burke–Fahn–Marsden Dystonia Rating Scale; NS, not significant.
[a]Patients with a worsening in motor symptoms; [b]improvement in motor scales.

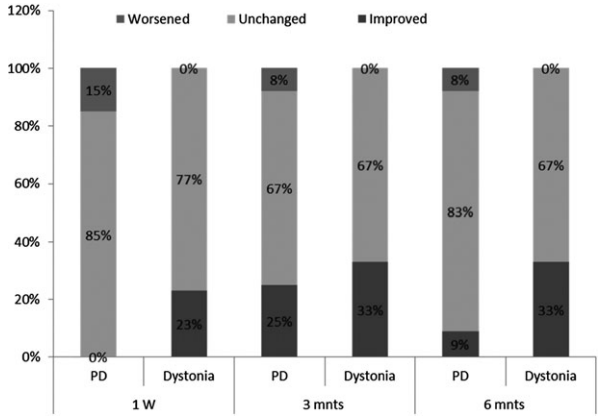

Figure 2 Patient CGI after 1 week and 3 and 6 months from replacement.

10 PD patients, $P > 0.05$) and the mean number of reprogramming sessions necessary to obtain the same clinical outcome after the replacement was 3.0 ± 1.4 (2.7 ± 1.2 for six dystonic patients, 3.2 ± 1.5 for 10 PD patients, $P = 0.34$) in 9.2 ± 6.0 days (8.1 ± 3.0 for dystonic patients, 9.7 ± 7.1 for PD patients, $P = 0.60$).

After the replacement with CC IPGs, a mean of 3.3 ± 1.2 reprogramming sessions were needed (2.8 ± 1.1 for dystonic patients, 3.3 ± 1.6 for PD patients, $P = 0.13$). No significant difference was found between the number of reprogramming sessions in CC versus CV mode, considering either the whole population or the different implant indications (whole, $P = 0.26$; dystonic patients, $P = 0.85$; PD patients, $P = 0.32$).

No adverse events due to surgical procedure were recorded. None of the patients presented side effects secondary to stimulation. Two PD patients reported a worsening in clinical condition with a rebound of tremor immediately after the replacement. In one case this worsening, related to under-stimulation, was solved by increasing the amplitude; in the second patient, tremor was controlled by changing the active contact. In the latter patient, the worsening was related to the high impedance (>4000 Ω) on the active contact, which made it impossible to increase the amplitude of stimulation up to a clinically effective value after the CC replacement. This is the only electrode dysfunction that occurred in our population after CC substitution.

A full discharge of Brio device occurred due to an insufficient training of the patient after the implant.

Programming parameters

Stimulation parameters are reported in Table 2. In PD patients, no significant differences between the programming settings and impedances before and after the replacement were found. In dystonic patients pulse width and impedances were comparable to pre-replacement status (Table 2), whilst frequency set in CC mode was significantly lower than that used in CV mode ($P = 0.016$).

Discussion

It is well known that after several years of chronic stimulation it is essential to maintain the previous outcome; therefore non-rechargeable IPGs for DBS need to be replaced within appropriate time frames in order to prevent complete battery drain and consequent rebound of clinical symptoms [17,18]. After CV IPG replacement, impedance of the stimulation circuit could change, producing a reduction or an increase of the current delivered to the target area. It is unknown whether these changes are clinically relevant: in some cases optimization of program settings may take days or weeks to reach the same clinical results obtained before the substitution [14,18].

To our knowledge this is the first assessment of the impact of replacement with CC mixed implants in patients previously stimulated chronically in CV mode. In the whole population examined (parkinsonian and dystonic patients) no significant difference was documented between pre- and post-CC replacement and the outcome remained stable at long-term follow-up.

However, amongst the six dystonic patients evaluated, the Burke–Fahn–Marsden Dystonia Rating

Table 2 Stimulation parameters before and after replacement

	Parkinsonian patients			Dystonic patients		
	Pre-replacement	Post-replacement	*P*	Pre-replacement	Post-replacement	*P*
Amplitude (V/mA)	3.3 ± 0.6	3.5 ± 1.6		2.8 ± 0.5	2.3 ± 0.6	
Pulse width (μs)	65.8 ± 12.1	68.7 ± 15.0	NS	135.0 ± 56.5	154.8 ± 56.6	NS
Frequency (Hz)	133.5 ± 36.1	130 ± 28.2	NS	138.3 ± 11.1	130 ± 0	0.016
Impedance (Ω)	821.3 ± 361.7	992.7 ± 664.5	NS	956.6 ± 550.1	1033.3 ± 462.8	NS
Total power (μW)	255.1 ± 88.99	181.6 ± 106.4	NS	319.5 ± 143.4	213.5 ± 57.5	NS

NS, not significant.

Scale score showed a trend to a further improvement of 8% after 3 months and of 10% after 6 months of CC stimulation. All these patients presented a multisegmental dystonia with prominent cranial (speech and swallowing difficulties) and cervical involvement, and this further, though small, clinical improvement had a greater impact on quality of life. The major improvements were obtained in four patients where CV stimulation reached suboptimal clinical results. In these cases, CC stimulation improved oromandibular condition, control of torcicollis and trunk, and dysarthria.

Even if this modification was observed only in a small case series, it could be speculated that this further clinical improvement could be related to transition to CC delivery allowing a more consistent stimulation distribution within brain tissue [8,10] essentially independent of the impedance fluctuations [19]. This is also what Lettieri *et al.* [6] observed comparing CC and CV stimulation in two groups of dystonic patients: the better clinical outcome obtained in the long-term follow-up only in patients treated in CC mode was probably due to a constant amount of charge delivered around the active lead.

Moreover in three dystonic patients some adverse effects related to CV stimulation, like dysarthria, improved soon after modification of the stimulation mode. Recently Cheung *et al.* [20] showed that in dystonic patients there is no correlation between clinical improvement and total electrical energy delivered to tissue, and a more tailored stimulation of correct regions could give better outcomes avoiding undesirable effects on neighboring structures.

Electrode dysfunctions and the leads' impedance augmentation seem to occur more frequently after IPG replacement [18]: a considerable rate of reduced clinical efficacy and/or intolerable side effects are described especially if high intensities are used before replacement [21]. Following CV replacements Allert *et al.* [18] showed that 20% of patients reported a worsening of clinical conditions although there was no evidence of technical problems; it was suggested that the decrease in symptom control was related to an altered current flow at the active contacts, with a consequent change in the volume of activated tissue. In our series the percentage of reported worsening was lower than that reported in the previous studies [16,19,22], and the rate of electrode dysfunction of 5%, corresponding to one case, was lower than that reported in the Allert *et al.* study [18]. Therefore CC IPGs could give physicians the possibility of delivering the effective therapy to the targeted nucleus, adapting the current flow to the impedance variation [8–13].

In our population no differences were seen between the number of reprogramming sessions required after CV and CC replacement to obtain the same clinical outcome.

It is worth mentioning that in all patients no serious adverse events occurred after the replacement, especially in terms of infections and pain at the pocket site. Contrasting with Pepper *et al.*'s data [23] no infection occurred in our patients after the battery changes. These results suggest that the insertion of adapters in the existing IPG pocket did not impact on the rate of infection, probably because it was not necessary to create a new pocket. After 6 months of follow-up, the majority of patients and physicians responded that they were satisfied with CC stimulation, in terms of both clinical outcome and aesthetic results.

All patients included in this data analysis had conventional CV devices before CC replacement and 31% of patients received a rechargeable neurostimulator. Of these patients none had any difficulty in managing rechargeable devices and all of them found the recharging procedure acceptable or comfortable. Also the patient who had a full discharge of Brio device in the training phase did not present any other trouble in the follow-up. Our results also confirm the compatibility of components made by different manufacturers.

Even if this analysis has several limitations (the small number of patients included, a short follow-up, the evaluation in a short interval after the replacement and the collection of impedance and programming settings just after the battery changes), this retrospective data collection adds new and interesting information about the use of CC devices as replacements of CV IPGs in terms of safety and efficacy and strengthens the scanty and sparse data on CV stimulation mode currently present in the literature.

Moreover our data show that the conversion from CV to CC devices could give the opportunity to optimize programming settings and better tailor the current delivered, compensating the impedance fluctuations.

As recently reported by Bronstein *et al.* [14], in our series as well as in other studies the main limitation on CC stimulation mode is the small number of patients included and the lack of blinded comparator trials. Future studies involving larger populations with a longer follow-up are necessary to confirm our experience about the impact of CC stimulation on clinical outcomes in dystonic and parkinsonian patients after chronic stimulation in the CV mode.

Acknowledgement

There is no acknowledgement and funding.

Disclosure of conflicts of interest

Dr Sensi was consultant to Boston Scientific and ABBvie; Dr Preda was consultant to Medtronic Italia, ABBvie and St Jude Medical.

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