TITLE: MULTICENTER EXPERIENCE OF MIXED DEEP BRAIN STIMULATION IMPLANTS FOR MOVEMENT DISORDERS

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DISCLOSURE OF CONFLICT OF INTEREST

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

ABSTRACT

Background. DBS devices rely on voltage-controlled stimulation, but now several current-controlled DBS devices are available. Constant current (CC) stimulation has been demonstrated to be effective in new implanted parkinsonian and dystonic patients, but the effect of modification from constant voltage (CV) to CC therapy in patients chronically stimulated with CV Implantable Pulse Generators (IPGs) for long time has not been assessed yet. The aim of this data collection is to report a multicenter experience in the replacements of constant voltage with constant current DBS devices from a safety and efficacy point of view.

Methods Nineteen patients underwent DBS IPG's replacements from CV to CC devices. Clinical features and therapy satisfaction were assessed before surgery, 1 week, 3 and 6 months after replacements. Programming settings and impedances were assessed before removing the CV device and when CC IPGs were switched on.

Results Clinical outcome of CC IPGs was similar to those obtained with CV devices and remained stable at 3 months follow-up. Impedance values recorded in CV and CC IPGs were similar. 95% of patients and physicians were satisfied with mixed implants. The rate of adverse events occurred after CC IPG replacement was comparable with that reported after CV IPG substitutions.

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

INTRODUCTION

Deep brain stimulation (DBS) is an established treatment for Parkinson's Disease (PD) and Dystonia also in a long term follow up [1-4]. 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 [5,6]. After CV IPG replacement, impedance of the stimulation circuit could change, producing the reduction or the increase of the current delivered to the target area and in some cases the optimization of program settings may last days or weeks to reach the same clinical results obtained before the substitution [5].

Traditionally DBS devices rely on voltage-controlled (CV) stimulation, delivering an adjustable voltage across the stimulating electrodes, essentially independent of stimulus current. Consequently, the therapeutic current and the volume of tissue activated in CV IPGs depend principally on the impedance of the tissue and the electrode-tissue interface [7-9]. Recent studies show that these impedances vary over time and over different time frames [10-15].

New constant current-controlled (CC) IPGs for DBS deliver constant current, automatically accommodating the voltage on the base of impedance variations [7,8,16], and are effective in new implanted parkinsonian and dystonic patients [8,16-19]. CC devices are used to replace depleted CV IPGs as well, and, through the use of an adapter, they can be connected to previously implanted leads and extensions. Such hybrid systems, in which "old" leads and extensions are connected to new CC IPGs, are referred as "mixed implant".

The aim of this data collection is to report our multicenter experience in the use of mixed implants from a safety and efficacy point of view.

METHODS

This multicenter study was performed between June 2013 and June 2014 and 19 patients undergoing DBS IPG's replacements from CV to CC devices were included in this data collection.

Since data was collected during routine clinical practice, no ethical committee approval was required. Patients gave consent to use their data.

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

After replacements in all CC IPGs were activate the same contacts setting used in the CV mode. The corresponding intensity to a given voltage delivered in CV implants before substitution was calculated by means of the “impedance therapy” values previously obtained with the use of the Medtronic DBS programmer (N’Vision).

Since there is not a perfect correspondence between pulse width values in CV and CC devices, after the replacement, in the new CC IPGs configuration, we chose to use the value immediately higher than the one present in CV setting. To compensate the increase in the pulse width, after the replacement, frequency was set to a value lower than the one programmed in the CV mode in order to obtain a similar total power value. To calculate this parameter (measured in microwatts), the following formula was adopted: $(V^2 \times PW \times F)/ Z$ for CV devices, and $(Z \times I^2 \times PW \times F)$ for CC devices where F is the frequency (measured in Hz), V is the voltage (measured in Volts), PW is the pulse width (measured in μs), Z is the impedance (measured in Ohms) and I is the current (measured in Ampere) [10,11,23,24].

For each patient the following data were collected:

- Number of replacements occurred before the replacement with a CC device
- Motor scores before and 3 months after the replacement: UPDRS III (Unified Parkinson’s Disease Rating Scale part III, ON Stim-ON Med) in PD patients, and Burke Fahn Marsden Dystonia Rating Scale (BFMDRS) in dystonic patients. For the comparison of clinical outcome before and after the CC replacements, the best motor scores obtained in CV stimulation mode were used as pre–replacement data. 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 [9].
- Mean battery duration between each CV replacement was collected, if other replacements occurred before the substitution from CV to CC IPGs,
- Number of programming sessions necessary to reach the same pre-replacement clinical outcomes after every substitution.
- Information about the programming settings and therapy impedances of IPGs before and after the replacement [20].
- Semi-structured interview to physicians and patients on clinical efficacy of CC stimulation, rated on a three-point CGI scale (improvement, no change, worsening) after 1 week, 3 and 6 months from the CC replacement.

- Patient's feedback about the recharging procedure after 6 months from the CC substitution in 6 of 19 patients, where rechargeable systems were chosen as replacement.

- Adverse events due to surgical procedure and side effects related to mixed implant.

- Total power delivered (TEED measured in μW), calculated as described above. As the two channels of IPGs are not overlapping in time, the total charge and total power were calculated independently for each lead and then added [8,9,21,22].

Continuous data are presented as mean ± SD. For all continuous collected variables, differences before and after replacement were evaluated by means of non parametric matched pairs Test of Mann-Whitney. All 2-tailed P values <0.05 were considered statistically significant. The STATA ver. 13 statistical package was used for the analysis.

RESULTS

In the data analysis 13 parkinsonian and 6 primary dystonic patients were included.

Three PD patients had never been submitted to IPG change before, the other 16 patients (6 dystonic and 10 PD patients) had already performed IPG replacements once (n= 13) or twice (n=3). Considering the whole population, the mean battery longevity of CV IPGs was 4.3±1.7 yrs (3.5±2.1 yrs for 6 dystonic pts, 4.9±1.3 yrs for 10 PD pts, 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 6 dystonic pts, 3.2±1.5 for 10 PD pts, p=0.34).

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

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

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

When improvement was stated, both neurologists and patients reported amelioration in motor performances, in particular, gait and phonation improved in 3 parkinsonian patients, and an amelioration of dysarthria and

improvement in motor tasks in 4 dystonic patients were observed. These results were maintained at 3 and 6 months.

Among side effects secondary to stimulation, 2 PD patients reported a worsening in clinical condition with a rebound of tremor immediately after the replacement. In one case the side effect was solved increasing the amplitude; in the second patient, tremor was controlled changing the active contact. In this latter patient, the worsening was related to the high impedance (>4000 Ohm) on the active contact, which made impossible to increase the amplitude of stimulation up to a clinically effective value after the CC replacement. This is the only electrode dysfunction occurred in our population after CC substitution.

After 6 months, 95% of patients and physicians would chose again a CC replacement, and 95% of patients was satisfied or fully satisfied of CC replacement.

A full discharge of BRIO occurred due to an insufficient training to the patient after the implant and an edema of the IPG pocket occurred two days after the implant, with spontaneous resolution.

All CV IPGs were conventional, whilst 33% (2 pts) of dystonic and 31% (4 pts) of parkinsonian patients were implanted with a rechargeable CC IPG. For 100% of patients the rechargeable procedure was acceptable (20%) or comfortable (80%).

Programming parameters

Stimulation parameters are reported in Figure 4.

In PD patients, no significant differences between the programming settings, impedances and TEED before and after the replacement were found. In dystonic patients impedances and TEED were comparable to pre replacement status (Fig. 4), while frequency set in CC mode was significant lower than that used in CV mode ($p=0.016$).

DISCUSSION

To our knowledge this is the first data collection that evaluated the impact of replacement to mixed implants with CC stimulation in patients initially stimulated in CV mode.

In parkinsonian patients UPDRS motor scores did not show any difference between pre and post CC replacement and remained stable at long term follow up.

In dystonic patients BFMDRS score showed a further improvement of 9% after 3 months of CC stimulation that is close to a statistical significance. Clinical improvement in dystonia following DBS surgery is often delayed, becoming evident after hours to several months after surgery [16,23] and could be due to progressive changes occurring at the electrode/brain interface and to significant and reversible decrease of impedance measured for the activated contact [5,12]. This is also what Lettieri et al. [8] observed comparing constant-current and constant-voltage stimulation in 2 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.

Electrode dysfunctions and the leads' impedance augmentation seem to occur more frequently after IPG's replacement [20,24]; a considerable rate of reduced clinical efficacy and/or intolerable side effects are described especially if high intensities are used before replacement [22]. Following CV replacements Allert et al. [5] showed that 20% of patients reported a worsening of clinical conditions although there were 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 of the volume of activated tissue (VTA).

In our series the percentage of reported worsening was lower than the one reported in the previous studies [18,20,22], and the rate of electrode dysfunction of 5%, corresponding to one case, was lower than that reported in the Allert et al. study [5].

It is also remarkable that in 3 dystonic patients some adverse effects related to the CV stimulation, like dysarthria, improved soon after the modification of stimulation mode. Considering the lack of significant difference of TEED between CV and CC stimulation, we think that the better clinical outcome after the IPG replacement, could be explained by the constant amount of charge delivered around the active lead, essentially independent of the impedance fluctuations [25].

Therefore CC IPGs could give to physicians the possibility to deliver the effective therapy to the targeted nucleus, adapting the current flow to the impedance variation [10-15].

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 worthy to mention that in our population no serious adverse events occurred after the replacement, especially in terms of infections and pain at the pocket side. Contrary to Pepper's data [29] no infection occurred in our patients after the battery changes. These results suggest that the insertion of adapters in the existing

IPG's 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 of CC stimulation, both in terms of 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 to manage rechargeable devices and all of them found the recharging procedure acceptable or comfortable.

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 data collection gave some essential information about the use of CC devices as replacements of CC IPGs in terms of safety and efficacy.

Our results suggest that the use of CC devices as replacement of CV IPGs is a safe and effective procedure. Moreover the conversion from CV to CC devices could give the opportunity to optimize programming settings and better tailor the current delivered, compensating the impedance's fluctuations. Future studies involving larger population 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 a chronic stimulation in CV mode.

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Figure 1 – Motor scores before and 3 months after replacement

	Before repl	3 months FU	P
UPDRS III	34.8±13.8	35.0±15.5	NS (0.74)
BFMDRS	25.3±13.5	23.1±12.8	NS (0.06)

Figure 2 – CGI reported by physicians after 1 week, 3, 6 months from replacement

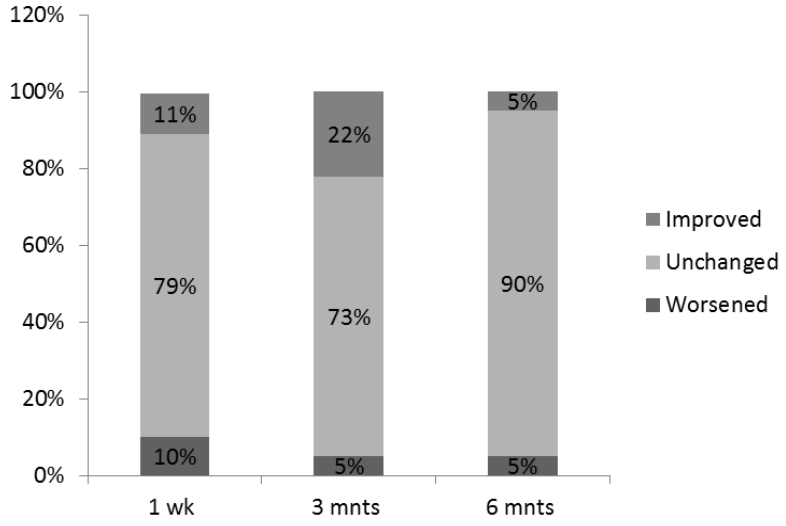

Figure 3 – Patient CGI after 1 week, 3, 6 months from replacement

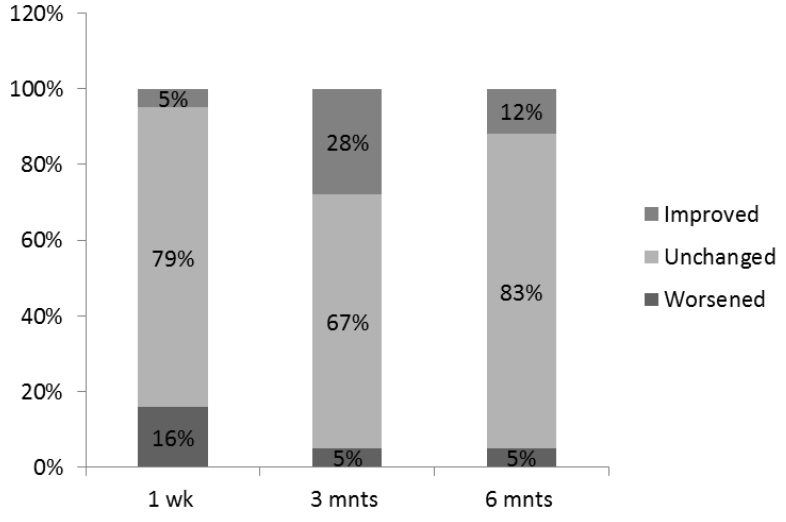

Figure 4 – Stimulation parameters before and after replacement

	Parkinsonian patients			Dystonic patients		
	Pre repl	**Post repl**	**P**	**Pre repl**	**Post repl**	**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