Brain Stimulation 9 (2016) 425–437

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Programming Deep Brain Stimulation for Parkinson's Disease: The Toronto Western Hospital Algorithms

Marina Picillo [a,b], Andres M. Lozano [c], Nancy Kou [a], Renato Puppi Munhoz [a], Alfonso Fasano [a,*]

[a] Morton and Gloria Shulman Movement Disorders Clinic and the Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital and Division of Neurology, University of Toronto, Toronto, Ontario, Canada
[b] Centre for Neurodegenerative diseases (CEMAND), Department of Medicine and Surgery, Neuroscience Section, University of Salerno, Salerno, Italy
[c] Division of Neurosurgery, University of Toronto, Toronto Western Hospital/University Health Network, Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Received 22 October 2015
Received in revised form 2 January 2016
Accepted 3 February 2016
Available online 12 February 2016

Keywords:
Parkinson's disease
Programming
Surgery
Stimulation-induced dyskinesia
Freezing
Speech

ABSTRACT

Background: Deep brain stimulation (DBS) is an established and effective treatment for Parkinson's disease (PD). After surgery, a number of extensive programming sessions are performed to define the most optimal stimulation parameters. Programming sessions mainly rely only on neurologist's experience. As a result, patients often undergo inconsistent and inefficient stimulation changes, as well as unnecessary visits.
Objective/hypothesis: We reviewed the literature on initial and follow-up DBS programming procedures and integrated our current practice at Toronto Western Hospital (TWH) to develop standardized DBS programming protocols. We propose four algorithms including the initial programming and specific algorithms tailored to symptoms experienced by patients following DBS: speech disturbances, stimulation-induced dyskinesia and gait impairment.
Methods: We conducted a literature search of PubMed from inception to July 2014 with the keywords "deep brain stimulation", "festination", "freezing", "initial programming", "Parkinson's disease", "postural instability", "speech disturbances", and "stimulation induced dyskinesia". Seventy papers were considered for this review.
Results: Based on the literature review and our experience at TWH, we refined four algorithms for: (1) the initial programming stage, and management of symptoms following DBS, particularly addressing (2) speech disturbances, (3) stimulation-induced dyskinesia, and (4) gait impairment.
Conclusions: We propose four algorithms tailored to an individualized approach to managing symptoms associated with DBS and disease progression in patients with PD. We encourage established as well as new DBS centers to test the clinical usefulness of these algorithms in supplementing the current standards of care.

Introduction

Deep brain stimulation (DBS) is an established and effective treatment for Parkinson's disease (PD). Three brain nuclei are on-label targets for DBS in PD: subthalamic nuclei (STN), globus pallidus pars interna (GPi) and ventral intermediate (Vim) nucleus of the thalamus [1]. After electrode(s) implantation, connection wires are internalized and connected to an implantable pulse generator (IPG) in the upper chest. Patients then participate in a number of extensive programming sessions to define the best stimulation parameters for optimal symptom management. Programming mainly relies on neurologist's personal experience, as no programming guidelines have been provided so far, with the exception of algorithms proposed by experts for the initial programming of PD patients [2–5]. Other sessions are very often organized during the follow-up visits in order to manage stimulation-induced side effects [e.g., speech problems and stimulation-induced dyskinesias] or the worsening of the underlying parkinsonism. While the usefulness of these reprogramming sessions is well established [6], no guidelines are available and most of these changes rely on the results of few open-label studies [1,7]. Indeed, although DBS has been in use for almost

Abbreviations: CCS, current-constant stimulation; DBS, deep brain stimulation; FOG, freezing of gait; GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; IPG, implantable pulse generator; MRI, magnetic resonance imaging; PD, Parkinson's disease; SNr, substantia nigra pars reticulate; STN, subthalamic nuclei; TEED, total energy delivered; TWH, Toronto Western Hospital; VCS, voltage-constant stimulation; Vim, ventral intermediate nucleus of the thalamus.

* Corresponding author. Tel.: +1 416 603 5800 ext 5961; fax: +1 416 603 5004.
E-mail address: alfonso.fasano@gmail.com (A. Fasano).

1935-861X/
http://dx.doi.org/10.1016/j.brs.2016.02.004

three decades, systematic programming protocols are still lacking, thus leading to inconsistent and inefficient stimulation adjustments, as well as numerous or unnecessary patients' visits. These issues compelled us to find ways to improve the efficiency of our programming sessions aimed at quality improvement of the process, thereby enhancing the patient's quality of care.

Here, we reviewed the literature on initial and follow-up DBS programming procedures and integrated it with our current practice at Toronto Western Hospital (TWH), in order to develop standardized DBS programming protocols to be shared with the scientific and medical community.

Methods

We searched published data in English language on the following topics: (1) initial programming; and (2) follow-up stimulation adjustments (for speech difficulties, stimulation-induced dyskinesias, freezing, festination and postural instability) from inception to July 2014 on PubMed. Keywords included "deep brain stimulation", "festination", "freezing", "initial programming", "Parkinson's disease", "postural instability", "speech disturbances", and "stimulation induced dyskinesia". Six hundred and sixty (660) papers were retrieved. Additional articles were recovered from recent reviews and reference lists of relevant publications. In total, 70 papers were taken into account for this review after excluding those not focused on movement disorders, preclinical studies and duplicated data. Results from the studies related to STN DBS management and considered to build the algorithms are summarized in Table 1.

Initial programming

Available data and recommendations

The only systematic evaluation of the impact of stimulation parameters on cardinal appendicular signs of PD was performed by the Grenoble group in 2002 [27]. The authors evaluated several combinations of settings, including pulse width (from 60 to 450 μs), frequency [from 5 to 185 Hz (Itrel II, Medtronic, Minneapolis, MN, USA) or 250 Hz (Kinetra, Medtronic)], and amplitude (from 1 V up to the highest tolerated value) and concluded that voltage followed by frequency was the most important factor in ameliorating parkinsonian signs [27].

Few papers – mainly driven by authors' own experience – detailed the basic algorithm for initial programming of DBS in PD [2–5].

The goal of the first programming visit after surgery is to determine the therapeutic window for each electrode contact, thus the lowest amplitude threshold for clinical benefits and the lowest amplitude threshold eliciting unwanted side effects [28]. It has been suggested that the initial programming visit should be performed off medication (MED OFF) after an overnight dopaminergic washout to assess the effects of DBS without the interference of medications [28].

Currently, there is debate on the timing of the first programming visit and practice among centers varies [28]. For instance, some teams initiate stimulation 2–3 or 4–5 weeks after hospital discharge [29,30] while others perform the initial programming during the hospitalization period [31]. Although this fast postoperative programming may be more cost-effective and convenient for patients, two important factors may bias the estimation of thresholds when programming is performed soon after surgery: (1) the effect of stimulation on motor symptoms may be covered by the insertional effect (i.e., the transient improvement induced by the mechanical placement of the electrode mimicking a lesion effect), especially after STN DBS [32]; (2) although strong evidence is still lacking, it is conceivable that the threshold for determining the therapeutic window may be biased due to the fluctuation of impedances in the early post-operative period (i.e., impedances are lower after electrode insertion due to the local edema and then higher over the first few days/weeks) [33]. The latter may have important clinical implications when using voltage-constant stimulation (VCS) whereby the current delivered to the tissue is inversely proportional to the electrode impedance [33]. Conversely, current-constant stimulation (CCS), which dynamically adjusts the current to adapt to changes in impedances of the tissue–electrode interface, might offer a more stable stimulation and thus preferred when performing the programming soon after surgery [34].

Indeed, the clinical effect of any programming algorithm is closely related to the electrode location and exclusion of surgical complications (i.e., bleedings, infections). Thus, post-operative neuroimaging is recommended possibly using approved magnetic resonance imaging (MRI) protocols [35]. Before initiating the programming, the impedances for each of the four electrode contacts should also be recorded under standard stimulation parameters to detect any hardware problems immediately following the implantation and to use as a reference for troubleshooting future hardware problems [4]. Then, the therapeutic window for each contact is determined keeping both the pulse width (60 μs) and frequency constant (130 Hz) and applying stepwise increase in amplitude (0.5 V) using a monopolar configuration (i.e., having the IPG as the anode and the contact as the cathode) [2,3].

Rigidity is the most useful sign to determine the benefit of stimulation because its severity does not fluctuate, it responds quickly to stimulation adjustments and it can be reliably examined, even if patient's cooperation is poor [2]. If rigidity is not present then bradykinesia or rest tremor may be used. Unfortunately, the time course of the stimulation response for bradykinesia is longer and is biased by fatigue and the patient's discomfort or expectations, and rest tremor may spontaneously fluctuate [2,3].

Focusing on one of these symptoms, amplitude is increased to determine the threshold for side effects, which can be *somatosensorial* (paresthesia), *motor* (muscle spasms, eye/gaze deviation, stimulation-induced dyskinesias or dystonia), *dysautonomic*, *behavioral* (depression, mania), or *unspecific* (confusion, malaise). Somatosensorial side effects are usually transient but may become permanent with high voltages. Unspecific side effects are only transient and may last few hours after the programming session. Remaining side effects demonstrate no habituation and are usually permanent at a certain threshold. Of note, stimulation-induced dyskinesias rarely occur during parameter adjustments, as they present with a latency of several hours. Finally, the contact with the largest therapeutic window is chosen to start the chronic stimulation, which is typically undertaken with a low amplitude (1.0 or 1.5 V) and slowly titrated in increments of 0.2–0.5 or more during the following days to reduce the risk of stimulation-induced dyskinesias and behavioral side effects [2,3].

There is considerable evidence that the active electrode contacts located either in proximity to the dorsal border of the STN or further dorsal within the subthalamic region are the most effective [36,37]. Regarding globus pallidus stimulation, contacts located in the dorsal GPi and in the GPi/GPe (globus pallidus pars externa) border are most often used [4].

Current limitations and TWH proposal

The initial programming of DBS devices can be a difficult and time-consuming process, requiring a highly trained and experienced individual to achieve desirable results [6]. Although other programming strategies based on local field potentials [38], neuroimaging [39,40], or computational models [41] have been proposed, there are no alternatives to classic manual programming to