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Before and after the veterans affairs cooperative program 468 study: Deep brain stimulator target selection for treatment of Parkinson's disease

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ABSTRACT

Introduction: The Veterans Affairs Cooperative Study Program 468 study (CSP 468) produced significant findings regarding deep brain stimulation (DBS) target selection for Parkinson's Disease (PD) treatment, yet its impact on clinical practices has not been described. Here we assess how CSP 468 influenced target selection at a high-volume movement disorders treatment center.

Methods: We compared DBS target site selection between 4-year periods that immediately preceded and followed CSP 468 publication. Additionally, we examined how baseline clinical features influenced target selection following CSP 468.

Results: The STN was the predominant site of DBS implantation before and after CSP 468 publication (93.2% of cases, and 60.4%, respectively), but GPi targeting increased significantly following CSP 468 publication (from 5.3% to 37.4%; $p < .001$). Patients who underwent GPi stimulation following CSP 468 exhibited worse indices of depression ($p < .001$), less responsiveness to medications ($p < .05$), and a trend towards worse pre-operative cognitive performance ($p = .06$). In multi-variate analysis, advanced patient age and depression were independent predictors of GPi targeting ($p < .01$).

Conclusions: Key findings of CSP 468 were reflected in our target selection of DBS for Parkinson's Disease. Following CSP 468, GPi targeting increased, and it was selected for patients with poorer cognitive and mood indices.

1. Introduction

Since the 1990s, when initial reports described the treatment of Parkinson's disease (PD) with deep brain stimulation (DBS), DBS has supplanted tissue lesioning as the primary surgical treatment for PD [1]. Randomized clinical trials have demonstrated the superiority of DBS for treating advanced PD, compared to best medical therapy alone [2,3]. Deep brain stimulation is recommended for patients who experience improved bradykinesia and rigidity with levodopa therapy, but who have developed debilitating motor fluctuations, dyskinesias, other medication side effects, or medication-resistant tremor. DBS is increasingly performed in PD patients with early motor fluctuations [4]. The principal motor signs of PD are thought to arise from dysfunction of the cortico-basal ganglia-thalamo-cortical loop [5]. The subthalamic nucleus (STN) and globus pallidus internus (GPi) are the principal targets for DBS treatment of PD [6].

A primary consideration in DBS treatment of PD is the selection of the STN versus the GPi as the site of electrode placement. A number of early clinical trials and retrospective studies attempted to guide clinical decision-making by assessing differences in patient outcomes between these two sites, but their findings were limited by small patient numbers and/or non-randomized designs [7–13]. While the STN was for many years treated as the default DBS target for PD, primarily due to findings suggesting long-term failure of GPi stimulation [9,14–16], this practice was significantly challenged by the results of the Veterans Affairs Cooperative Studies Program 468 (here referred to as 'CSP 468'), which was a multi-center, randomized, blinded trial of STN versus GPi DBS for treatment of PD

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CSP 468, which described patient outcomes at 24 and 36 months post-implantation, noted equivalent and stable improvements in the Unified Parkinson's Disease Rating Scale-III (UPDRS-III) scores between STN and GPi implantations [17,18]. Additionally, at 24 months, no significant differences in patient-reported function or adverse effects were noted. Patients who underwent STN stimulation, however, required lower doses of dopaminergic medications than those who underwent GPi stimulation. By contrast, in assessments of neurocognitive function, STN stimulation was associated with a worsening of visuo-motor processing, while GPi stimulation was not. At 24 months, depressive symptoms were found to be worse with STN stimulation, and improved with GPi stimulation. At 36 months, patients who underwent STN stimulation exhibited worse scores on the Mattis Dementia Rating Scale and the Hopkins Verbal Learning Test, though these findings may have been confounded by slight differences in pre-operative neurocognitive function between the STN and GPi groups.

As CSP 468 represents the largest randomized comparison of DBS implantation sites in PD, it has significantly shaped the discussion around DBS target selection [6,19,20]. In general, its results suggest that patient-specific consideration of cognition, mood, and patient tolerance of medication side effects should guide the choice between STN versus GPi targets [6,17,18]. However, to date there has been no retrospective study that examines or demonstrates how target selection may have evolved in response to CSP 468. Here we have compared our institution's practice patterns before and after the publication of CSP 468, in order to assess its influence on target selection for DBS treatment of PD.

2. Methods

2.1. Study population

All patients underwent DBS treatment for PD at a single hospital, which was the primary surgical site for the University of California, San Francisco, Movement Disorders and Neuromodulation Center. All procedures were performed by one of two senior surgeons (P.A.S. or P.S.L.). Our institutional review board approved the use of patient medical information for the purposes of this study.

The determination of target site, as well as selection of bilateral versus unilateral lead implantation, and awake versus asleep surgical method, were made following a multidisciplinary meeting in which each patient's medical, surgical, social, and medication histories, as well as on/off medication motor examination and neuropsychological evaluation were thoroughly discussed. Awake surgeries were performed using a Leksell frame, while asleep surgeries were performed using interventional MRI and a skull-mounted aiming device (NexFrame, 2006 to 2010 [21], or SmartFrame, 2010 to 2014) [22,23]. Patients who had undergone prior lesioning procedures for PD were excluded.

To assess the rates of STN and GPi implantations before and after CSP 468 (published July, 2010), we examined the population of patients who underwent DBS during either the four-year period preceding publication of CSP 468 study (i.e., July, 2006 to June, 2010), or during the four-year period that followed its publication (July, 2010 to June, 2014). We also compared how baseline clinical features varied between patients who underwent STN versus GPi targeting after the publication of CSP 468.

2.2. Patient clinical characteristics

Patient information was collected through review of electronic medical records. This included patient age, sex, implantation site, number of leads implanted (ie, unilateral versus bilateral), and surgeon (P.A.S. or P.S.L.). Additionally, for patients who underwent DBS procedures following CSP 468 publication, (ie, July, 2010 to June, 2014), we also recorded disease duration, levodopa equivalent dose (LEED) values, Montreal cognitive assessment (MoCA) scores, off-medication and on-medication UPDRS scores, Beck Depression Inventory 2 (BDI) scores, and Beck Anxiety Inventory (BAI) scores. Due to disease severity, some patients could not complete all tasks involved in the MoCA, therefore, MoCA scores were expressed as a fraction of the individual patient's maximum possible score ('MoCA percentage').

2.3. Statistical analyses

Prior to analyses, variables were examined for outliers. Two-sample t-tests or non-parametric equivalent in unadjusted analyses were applied for continuous variables. Chi-square tests in unadjusted analyses were used to compare categorical variables. Since the findings reported are considered exploratory, correction for multiple comparisons was not performed.

Uni-variate and multi-variate analyses were performed using JMP Pro statistical software (version 12.0.1). Continuous data were partitioned into categorical groups via univariate classification and regression trees. Logistic regression multivariate models were built using a mixed forward/backward step-wise selection process, with p-value threshold criteria for inclusion and exclusion of 0.25 and 0.05, respectively.

3. Results

A total of 133 patients were included in the group that underwent DBS before CSP 468, and 182 were included in the group that underwent surgery after CSP 468 (Table 1). The STN was the most frequently implanted site both before (93.2% of patients) and after (60.4%) CSP 468. However, there was a statistically significant increase in the rate of GPi implantation following publication of CSP 468 (Fig. 1). During the four-year period preceding CSP 468, the GPi targeting was performed in 5.3% of cases, while in the following four years, the GPi targeting was performed in 37.4% of cases ($p < .001$). Very rarely, DBS leads were implanted in the pedunculopontine nucleus or thalamus (each was targeted once before CSP 468 (0.8%, each)), while four patients (2.2%) underwent targeting of the thalamus during the period following CSP 468. These patients were excluded from our analysis.

Overall, we did not observe significant differences in patient age, sex, or operating neurosurgeon between the groups that underwent surgery before versus after CSP 468 (Table 1). Bilateral lead implantations were performed more frequently than unilateral implantations both before (88.7% of cases) and after (67.6%) CSP 468. However, a significant increase in the rate of unilateral procedures occurred after CSP 468 (11.3% of cases before, versus 32.4% after; $p < .001$). Additionally, during both periods, awake, physiologically-guided DBS implantation was performed more frequently than lead implantation using interventional MRI under general anesthesia, but it was more common before CSP 468 (82.0% before, and 54.4% after; $p < .00001$). The significant increase in the rate of procedures that were performed with the patient asleep (18.0% of cases before, versus 45.6% after) coincided with our implementation of a second-generation interventional MRI system around the time of CSP 468 publication [22,23].

To assess whether key findings of CSP 468 were reflected in our selections of DBS targets, we compared features between patients who underwent STN versus GPi implantation during the period following CSP 468 (Table 2). We found that patients who underwent GPi implantation were older than those who underwent STN implantation (65.1 ± 6.1 years, versus 61.7 ± 7.6, respectively;

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