Archival Report

Biological Psychiatry

A Randomized Sham-Controlled Trial of Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Chronic Treatment-Resistant Depression

Darin D. Dougherty, Ali R. Rezai, Linda L. Carpenter, Robert H. Howland, Mahendra T. Bhati, John P. O'Reardon, Emad N. Eskandar, Gordon H. Baltuch, Andre D. Machado, Douglas Kondziolka, Cristina Cusin, Karleyton C. Evans, Lawrence H. Price, Karen Jacobs, Mayur Pandya, Timothey Denko, Audrey R. Tyrka, Tim Brelje, Thilo Deckersbach, Cynthia Kubu, and Donald A. Malone Jr.

ABSTRACT

BACKGROUND: Multiple open-label trials of deep brain stimulation (DBS) for treatment-resistant depression (TRD), including those targeting the ventral capsule/ventral striatum target, have shown encouraging response rates. However, no randomized controlled trials of DBS for TRD have been published.

METHODS: Thirty patients with TRD participated in a sham-controlled trial of DBS at the ventral capsule/ventral striatum target for TRD. Patients were randomized to active versus sham DBS treatment in a blinded fashion for 16 weeks, followed by an open-label continuation phase. The primary outcome measure was response, defined as a 50% or greater improvement on the Montgomery–Åsberg Depression Rating Scale from baseline.

RESULTS: There was no significant difference in response rates between the active (3 of 15 subjects; 20%) and control (2 of 14 subjects; 14.3%) treatment arms and no significant difference between change in Montgomery–Åsberg Depression Rating Scale scores as a continuous measure upon completion of the 16-week controlled phase of the trial. The response rates at 12, 18, and 24 months during the open-label continuation phase were 20%, 26.7%, and 23.3%, respectively.

CONCLUSION: The results of this first randomized controlled study of DBS for the treatment of TRD did not demonstrate a significant difference in response rates between the active and control groups at the end of the 16-week controlled phase. However, a range of 20% to 26.7% of patients did achieve response at any time during the open-label continuation phase. Future studies, perhaps utilizing alternative study designs and stimulation parameters, are needed.

Keywords: Deep brain stimulation, DBS, Treatment resistant depression, TRD, Major depression, Ventral capsule/ventral striatum

http://dx.doi.org/10.1016/j.biopsych.2014.11.023

Major depressive disorder (MDD) is the third leading cause of disability in the world (1). While most patients with MDD achieve benefit from conventional antidepressant treatments, a significant minority do not respond to sequential trials of various drug therapies, psychotherapies, and/or electroconvulsive therapy (ECT) (2). These patients are described as having chronic treatment-resistant depression (TRD). Neurosurgical interventions, including ablative procedures such as anterior cingulotomy, anterior capsulotomy, subcaudate tractotomy, and limbic leucotomy have been employed for patients with TRD for decades. Reported outcomes have varied, with some studies showing benefit in up to two-thirds of patients with TRD (3–5).

Deep brain stimulation (DBS) entails the direct application of electrical energy via electrodes surgically implanted in deep brain structures, and is an accepted neurosurgical intervention for various movement disorders. More recently, DBS has been investigated as a potential neurosurgical intervention for psychiatric patients with obsessive-compulsive disorder (OCD) and TRD. Relying on the same devices and procedures used to treat movement disorders and OCD, different research groups have investigated the potential antidepressant efficacy of DBS at various anatomical targets including the ventral capsule/ventral striatum (VC/VS), subgenual cingulate cortex (Cg25), nucleus accumbens, medial forebrain bundle, and lateral habenula (6–15). Since the early 1960s, the VC/VS territory has been identified as a critical target for anterior capsulotomy, an ablative procedure, primarily utilized to treat intractable OCD (16). Given the efficacy of anterior

SEE COMMENTARY ON PAGE 218

 ISSN: 0006-3223

capsulotomy for OCD, the anterior capsulotomy target was chosen in the first report of the use of DBS for a psychiatric illness. Nuttin and colleagues reported that three of their four patients with OCD benefited following DBS in the anterior limb of the interior capsule (17). Subsequently, this target was studied and gradually modified to the current VC/VS target by multiple groups. The pooled data from these groups (18) led to the first approval of DBS for treatment of a psychiatric illness, OCD, by the United States Food and Drug Administration under a humanitarian device exemption. During these studies of VC/VS DBS in patients with intractable OCD, it was serendipitously noted that the subjects' comorbid depressive symptoms also markedly improved. This finding was not entirely unexpected given the overlap of the circuitry implicated in the pathophysiology of MDD and OCD. These observations led to an initial open label trial of VC/VS for TRD (11). The subsequent positive results of this open trial led to the controlled trial reported in this manuscript.

Thus far, all published DBS data describing treatment of TRD have been from uncontrolled open-label studies. The subjects in these studies were followed for one to six years. At the last follow-up across all studies, response rates varied from 29% to 92% and remission rates varied from 33% to 58%. One particular open-label study of VC/VS DBS for TRD demonstrated a 53% response rate and a 40% remission rate at time of last follow-up assessment (11). Based on these findings, a multicenter, randomized double-blind sham-controlled trial of VC/VS DBS for TRD with the objective to demonstrate active stimulation is better than no stimulation was conducted. Here we describe the results from the first randomized controlled clinical trial ever reported for DBS as a treatment for TRD.

METHODS AND MATERIALS

This prospectively designed investigation was sponsored by Medtronic, Inc. and represents a collaborative effort between the departments of Psychiatry and Neurosurgery at the Cleveland Clinic, University of Pittsburgh, University of Pennsylvania, Butler Hospital/Brown Medical School, and the Massachusetts General Hospital. Institutional Review Board approval was obtained at each site.

Patient Selection

Study procedures were identical at each site. Patient referrals to each site came from within and outside the five study centers. All available medical records were obtained and reviewed before evaluations were performed to determine study eligibility.

Inclusion Criteria. Subjects signed a Screening Consent Form prior to conducting any study-related screening procedures. Following successful completion of the screening phase, subjects signed a Study Informed Consent Form prior to the initiation of any other study-related procedures. Subjects were ≥18 years of age and met Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) diagnostic criteria for MDD. Medical record documentation that each patient's current major depressive episode had persisted for ≥2 years was required. Treatment resistance was defined as lack of clinically substantive response to 4 or more adequate trials of antidepressant therapy as determined by use of a modified version of the Antidepressant Treatment History Form (ATHF; 19). Three of these 4 trials had to have occurred in the current depressive episode. One of these 4 trials had to include a combination of 2 or more antidepressant medications from 2 different antidepressant classes. One of these 4 trials had to have included 1 of the following augmentation agents: lithium, triiodothyronine, buspirone, pindolol or an atypical antipsychotic. One of the 4 trials may have included a complete course of ECT. All subjects must have received ≥6 weeks of psychotherapy treatment, for the current or a previous depressive episode, without significant improvement. Subjects' psychiatric treatment regimen was kept unchanged for ≥30 days prior to the study screening Montgomery–Åsberg Depression Rating Scale (MADRS). The subjects' required screening MADRS score was ≥28. The baseline MADRS score was performed after initial screening and was required to be ≥26. Female subjects of child-bearing potential had to use a medically acceptable method of contraception throughout participation in this trial.

Exclusion Criteria. Subjects could not meet DSM-IV criteria for bipolar disorder, any psychotic disorder or psychotic symptoms, OCD, or a current Axis I disorder that was primary to the MDD. Personality disorder diagnoses did not exclude potential subjects unless it was the site investigator's opinion that this would adversely impact subject compliance or safety during the study. Subjects could not have a DSM-IV diagnosis of panic disorder, posttraumatic stress disorder, eating disorder, or substance use disorder ≤6 months prior to the screening, could not meet DSM-IV criteria for any substance dependence within the 12 months prior to screening, and could not pose an imminent suicide risk. Subjects with common contraindications for surgery such as major medical comorbidities or use of anticlotting medications that could not be discontinued were also excluded.

Surgical Procedure

Electrodes were implanted bilaterally in the VC/VS using stereotactic frame-based, magnetic resonance technique as previously described using Medtronic 3391 leads (11). Leads were considered "in the target" if the most distal contact, second most distal contact, or the interspace between these was located within the following boundaries: X-axis = 5–10 mm lateral to the midline, Y-axis = 0–5 mm anterior to the posterior border of the anterior commissure, and Z-axis = 1–5 mm inferior to the intercommissural line. An analysis was conducted to determine that each surgeon placed the lead as planned under protocol.

Intraoperative test stimulation was performed after lead implantation, with the patient awake and able to respond to questions, at different contact points on the implanted electrodes. Subjective qualitative responses were used to assess for positive or negative effects on mood, anxiety, or energy prior to fixing the leads into position. Intraoperative stimulation was primarily designed to assure that the subject could tolerate stimulation without side effects at the targeted lead location.