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Stimulation of the motor cortex for disabling essential tremor

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Abstract

Objective: To examine the safety and efficacy of targeted stimulation of the motor cortex as a treatment for essential tremor (ET).
Patients and methods: At the University of Kansas Medical Center, two patients with essential tremor received stimulation of the (contralateral) motor cortex using an investigational implantable pulse generator (IPG). Patients were evaluated with the Fahn Tolosa Marin tremor rating scale (TRS) at baseline, 1 week and 4 weeks after surgery, both with stimulation turned on and turned off. Both patients also received neuropsychological assessments at baseline and again after surgery.
Results: Patient 1 was a 75-year-old male with tremor for 20 years. His baseline total TRS score was 61 and his TRS 1 month after surgery was 57. His IPG was set at 30 Hz, 3 mA and 250 μs pulse width. Patient 2 was a 60-year-old male with tremor for over 10 years. His baseline total TRS was 47 and it was 43, 1 month after surgery. His IPG was set at 50 Hz, 5 mA and 250 μs pulse width. There were no adverse effects.
Conclusion: Cortical stimulation of the primary hand motor cortex contralateral to the dominant hand was ineffective for the treatment of ET with the stimulation parameters used in this study. Future research examining other stimulation parameters is necessary to determine if there is a role for cortical stimulation in the treatment of ET.

Keywords: Essential tremor; Cortical stimulation; Motor cortex stimulation

1. Introduction

Essential tremor (ET) is one of the most common movement disorders and can be quite disabling in some patients. Although there are pharmacological treatments that are effective for some patients, in approximately 50% of patients these treatments are not successful [1]. In patients with disabling medication resistant ET, deep brain stimulation (DBS) of the ventral intermediate nucleus of the thalamus can be an effective treatment. However, DBS is a highly invasive surgical procedure and can have potentially serious adverse events. Electrical stimulation of the motor cortex has been reported to be effective in the treatment of Parkinsonian tremor. Similar to DBS, the electrode contact strip is connected by an extension wire tunneled down the neck to an implantable pulse generator (IPG) located in the subclavicular region of the chest. In contrast to DBS, stimulation of the motor cortex does not require any contact with or penetration of brain tissue as the device is placed above the dura possibly resulting in fewer serious adverse events; the procedure is done under general anesthesia so the patient is not awake for the procedure, and the procedure takes approximately 1 h and does not require neurophysiological mapping, placing less stress on the patient.

Canavero et al. [2,3] demonstrated in three patients with Parkinson's disease that unilateral stimulation of the primary motor cortex effectively reduced tremor and rigidity bilaterally without serious adverse events. These results were confirmed in a larger series of 16 Parkinson's disease patients that received primary motor cortex stimulation [4]. In this report, 10 of 16 patients showed benefit in Parkinsonian symptoms after the procedure. Only one patient failed to show benefit and the other five had received stimulation for a period too short for complete evaluation. Nguyen et al. [5] reported a case with facial pain and upper extremity action tremor due to removal of an acoustic neurinoma in which chronic cortical stimulation resolved both the facial pain and the action tremor. This effect was maintained throughout a 32-month follow-up. There have been no reports to date of motor cortex

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stimulation as a treatment for ET. Therefore, the objective of this study was to evaluate the safety and effectiveness of electrical stimulation of the motor cortex with a specified stimulation protocol for the treatment of ET.

2. Methods

2.1. Patient population

Two ET patients from the Movement Disorder Center at the University of Kansas Medical Center underwent unilateral motor cortex stimulation. The inclusion criteria included medically resistant ET defined as the presence of disabling postural and/or kinetic tremor despite medical therapy with propranolol or primidone or an inability to tolerate ET medications, the presence of disabling tremor as measured by a score of 3 out of 4 on the Fahn Tolosa Marin tremor rating scale for postural or kinetic tremor of the targeted limb, no other unstable medical conditions, age less than 80 and a willingness to complete follow-up evaluations. Exclusion criteria included a diagnosis of ET for less than 3 years, history of seizure disorder, pregnancy or intent to become pregnant during the study, moderate to severe dementia, active psychiatric illness, currently taking medication known to induce tremor (e.g., valproate, tricyclic antidepressants, steroids, lithium, amphetamine derivatives, beta agonists, theophylline, cyclosporine, amiodarone), presence of other medical conditions causing tremor (e.g., hyperthyroidism, hyperparathyroidism, Wilson's disease, B12 deficiency, renal failure, pheochromocytoma, alcohol withdrawal, other CNS disease or injury), any medical condition that may increase the risk of the surgery, botulinum toxin injections within the last 6 months, current alcohol or drug abuse, and previous neurosurgery for ET. The study was approved by the Food and Drug Administration (FDA) and the University of Kansas Medical Center's Institutional Review Board and both patients provided written informed consent for participation in the study. The investigational device system was provided by Northstar Neuroscience, Seattle, WA.

2.2. Imaging and surgical procedures

Prior to randomization structural magnetic resonance imaging (MRI) was done to rule out other causes of tremor, and functional MRI (*f*MRI) was done to identify the target cortical area associated with movement of the subject's hand and fingers since tremor was most pronounced in the upper extremity. Patients performed a finger-tapping task using their dominant hand while alternating between rest and active performance of the motor activity. The cortical area identified by the *f*MRI was used to guide selection of the site of electrode placement and cortical stimulation. Data from the imaging studies were transferred to a stereotactic neuronavigation system.

Patients received a single pre-operative prophylactic antibiotic dose. Under general anesthesia, hair was shaved and skin prepared for electrode placement contralateral to the subject's dominant hand. An investigational strip electrode containing two platinum–iridium contact elements encased in a flexible silicone sheath was placed over the middle portion of precentral cortex over primary motor hand cortex. The distal contact element was the anode and the proximal contact element was the cathode. The exposed area of an electrode contact was 3 mm in diameter and they were spaced 31 mm apart. The total dimension of the electrode was approximately 10 mm × 45 mm. Two burr holes (approximately 1.5 cm in diameter) were placed above the predetermined area of the cortex, as guided by the stereotactic neuronavigation. The cortical stimulation electrode was slid into one burr hole and pulled through the other so that it was placed epidurally over the primary motor cortex. The electrode was placed parallel and slightly anterior to the central sulcus so that it was positioned to stimulate the brain hemisphere contralateral to the subject's dominant hand experiencing tremor. Intraoperative testing was done to confirm electrode placement and lead integrity. The electrode was then anchored to prevent migration.

Using standard tunneling procedures, the electrode leads were tunneled beneath the scalp and the skin of the neck, and connected to the subclavicularly implanted pulse generator (IPG). The investigational IPG was an implantable, multi-programmable, bipolar generator that delivers electrical stimulation. The IPG was housed in a hermetically sealed titanium case and is powered by a single battery. The 25-g IPG measures 52 mm × 52 mm × 6.9 mm. The stimulation system was tested after electrode lead tunneling to ensure continuity of the system. The initial incision wounds were irrigated and closed. Patients remained in the hospital overnight so the surgical site could be closely observed for wound healing and potential infection.

2.3. Programming

The IPG was programmed (pulse repetition frequency, pulse duration, and current level) at week 1 and again readjusted at week 4 if necessary. The programming procedures were based on a detailed protocol described below which was based on previous experience with cortical stimulation for movement disorders [2,3]. The optimal stimulation frequency and current level was initially assessed at a pulse duration of 250 μs by delivering a 1-min pulse train at 20 Hz and 2 mA which was gradually increased to a maximum current of 6.7 mA. The short-term effect of each setting on postural and kinetic tremor was recorded and there was a 1-min washout period between changes. Following the 20 Hz assessments, stimulation frequency was incremented stepwise up to 127 Hz and the best current in reducing postural and kinetic tremor was determined for each frequency. Once the optimal frequency and current were determined for the pulse duration of 250 μs, then a pulse duration of 130 μs was