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Effects of deep brain stimulation on seizure number and signal synchrony in epileptogenic brain regions

A. Study Purpose and Rationale

Epilepsy is categorized as any of various disorders marked by repetitive aberrant electrical activity in the central nervous system and typically manifested by convulsive attacks known as seizures. It is estimated that approximately 1%-2% of the world's population may be afflicted with epilepsy, making it among the most common of neurological disorders (Engel, 1989; Engel & Pedley, 1997). The hallmark of epilepsy is recurrent seizures. Recurrent seizures may occur as a result of a large number of causes and the underlying mechanisms frequently are not fully understood. If seizures cannot be controlled, the patient may experience major disruptions in family, social, educational and vocational activities that can have profound impacts on their quality of life (Goldstein & Harden, 2000). The mainstay of treatment is chronic medication based on modulation of cortical inhibition/excitation balance to prevent seizures. Anticonvulsant drugs help about two-thirds of epilepsy patients achieve effective seizure control. The remaining approximately one-third are refractory to pharmaceutical therapy (Fisher, 1998). Furthermore, many patients develop a tolerance to the anticonvulsant effects causing a marked decrease in drug efficacy. In addition, these drugs frequently have many concomitant side effects such as dizziness, drowsiness, impaired vision, headache, mood change, rash and weight gain.

A study supported by the Epilepsy Foundation estimated the annual financial cost of epilepsy to be approximately $12.5 billion, $11.1 billion of which is due to newly diagnosed patients with poorly controllable seizure syndromes (Begley and Beghi, 2002). Because of the difficulty in treating such a large population of patients and the overall cost of individuals with medically and surgically refractory seizure syndromes, it is clear that alternative treatments are necessary. To this end, numerous researchers have turned their attention to exploring therapeutic stimulation as a possible treatment for medically refractory epilepsy syndromes. There have been two large-scale clinical trials for stimulation in epilepsy. The first was the SANTE trial by Medtronics. This study was a multi-center, randomized, double-blind trial of bilateral anterior thalamus stimulation in 110 patients with medically refractory partial and secondarily generalized seizures. They found that after 3 months of stimulation, the treatment group had a 29% greater decline in seizure frequency as compared to the control (implanted but not stimulated) group and a 54% reduction in seizures at 2 year follow up for all pooled participants. Stimulation parameters consisted of 5V using 90 microsecond pulses at 145 Hz with one minute on and 5 minutes off. The first three months were blinded, the following 9 months were unblinded and all participants received stimulation and the following year all stimulation parameters

were allowed to be adjusted by clinicians ad lib (Fisher, et al, 2010). Somewhat superior outcomes (37.9% reduction in seizures after 3 months) were found in the NeuroPace multicenter randomized double-blind pivotal trial that utilized stimulation at the seizure focus of 191 patients with medically intractable multifocal seizure. Stimulation was triggered by seizure dynamics recorded in subdural electrodes (Morrell, et al, 2011). This trial showed not only slightly improved outcomes (37.9% seizure reduction in the stimulated versus 17.3% in the unstimulated group), but also utilized a semi-closed loop algorithm in that it only delivered stimulation when seizures were detected.

For some patients, surgery may be another option by having the focus generating a partial seizure electrically mapped and surgically removed. While surgery is successful in preventing seizures in about 8% of the total epileptic patients (Engel et al., 1993; Tellez-Zenteno et al., 2005), there are legitimate fears of possible surgical complications as well as neurological deficits such as memory loss or cognitive impairment. Also, the excision of an epileptogenic focus becomes impractical or inefficacious in patients with multiple foci, generalized seizures or foci located too close to eloquent tissue (such as language centers). Finally, surgery techniques are anatomically irreversible. Such intractable epilepsy, both resistant to drug treatment and unsuitable for surgery, is a significant public health problem so that other alternative therapeutic approaches are needed. Stimulation can have the advantages of reversibility and adjustability for maximizing efficacy. In addition, it has the potential to be used in patients who would not otherwise be thought of as candidates for surgery. Furthermore, no brain tissue is destroyed and the stimulator can theoretically be adjusted to achieve the best outcome. It can also be turned off or removed if adverse side effects occur. However, in order to maximize efficacy of neural stimulation, it is important to consider the underlying dynamics of the system we wish to control, in this case, epilepsy.

Unlike cardiac pacemakers that regulate a rhythmic heartbeat, the brain is a much more complicated dynamical system with trillions of neurons firing in complicated and asynchronous patterns that require much more complex stimulation protocols to manipulate. In open loop control, without any feedback information, the stimulation is typically turned on and off periodically following preset programming regardless of the underlying brain state. However, the exact nature and timing of these cycles are sometimes very critical. Under normal conditions in which no pathological state is present, chronically stimulated neurons could easily get fatigued under such long-term activation resulting in alteration of normal brain function. Alternatively, constant stimulation could lead to either an alteration in synaptic efficacy in the affected region thereby changing network characteristics in possibly a deleterious way such as by kindling new seizure activity or potentially by decreasing stimulation efficacy local to the electrodes.

However, a more complex and subtle relationship between limbic structures and thalamus may exist that could be taken advantage of with a more adaptive form of therapeutic electrical stimulation. In particular, if synchronization patterns can be identified between critical brain nuclei taking part in seizure maintenance, one may be able to abolish this activity by interrupting the pathologically synchronous relationship.

Although a number of studies in humans and animals have shown some success in controlling seizures using therapeutic stimulation, no human trials have attempted to utilize features of the seizure dynamics to determine stimulation parameters. Such an approach may be termed closed-loop stimulation in that, ideally, a device might be designed that is fully implantable (no external hardware) and utilizes features recorded from a seizure and dynamically determines the response stimulation pattern to revert the pathological network to a non-seizure state. It is proposed here that a stimulation protocol that determines feedback stimulation characteristics (i.e. timing, frequency, duration, amplitude, and power) from the signals recorded from the underlying seizure itself, with triggering of stimulation based on seizure timing will be the most efficacious in decreasing seizure number in patients with medically intractable focal seizure syndromes.

B. Study Design and Statistical Analysis

Study participants will initially be randomized to either the stimulation (treatment) condition or the control (sham electrode placement) condition for three months. Following that, there will be an unblinded 6 month trial where all participants will receive stimulation. Participants will be followed for 2 years.

For an effect size of 25% more reduction in seizures in the stimulated versus the control group after three months of stimulations and a 50% reduction in seizures in all stimulated subjects, 60 patients will power the study at 80% with a p value of < 0.05 for paired t-test analysis.

Primary efficacy will be demonstrated by reduction in monthly seizure rate (from seizure diaries) from baseline in the treatment versus control group using paired t-test for percent change of seizures from baseline.

Secondary clinical outcomes will include Quality of Life in Epilepsy (QoLIE-31) score, Liverpool Seizure Severity Scale (LSSS) and neuropsychological testing before, once during the three-month blinded period and once in the three months following unblinding.

Secondary research outcomes will include blinded analysis of the synchronization levels throughout the study duration using the same synchronization algorithm that determines feedback stimulation parameters. This data will be continuously collected via the implanted device and offloaded periodically during clinical visits with device interrogation throughout the study period.

C. Study Procedure

Patients included in the study will have preliminary focus identification via 24-hour scalp EEG monitoring. Following this, the focus (foci) will be further characterized via implantation of subdural grid electrodes in the hemisphere of seizure focus (as identified by scalp EEG). Patients will then be monitored in a continuous epilepsy monitoring unit for a period of one-week to full identify and characterize the seizure focus (foci). Once identified, a depth stimulating electrode will be stereotactically implanted in the focus (foci) with subdural electrodes left in place for recording of the seizure activity.

Patients will then be randomized to either the control (sham) or treatment condition. Investigators and care personnel will be blinded as to their condition. Stimulus artifacts will be automatically removed via the onboard software to ensure blinding of on and offline data analysis as well as to blind caregivers when interrogating the system device. This information will be made available during the unblinded period of the study.

Patients will be stimulated or not (control) for a period of three months. Following this, all subjects will be stimulated for a period of 6 months. All patients will be followed for a period of 2 years. Stimulation will only be delivered when the onboard analysis software detects a seizure. This will utilize standard protocols for detection (*not* prediction) of seizure onset with learning algorithms. Stimulation parameters will be determined using the onboard synchrony analysis software delivering phase-resetting stimulation when a seizure is detected.

D. Study Drugs

No study drugs are proposed.

E. Medical Device

Components of the device include the following:

(1) Subdural electrodes (standard for epilepsy localization surgery)
(2) Depth electrodes (proprietary designed stimulation electrode)
(3) Software (onboard chip and offline software) based off of Fine et al, 2010.

(4) Interrogation wand
(5) Patient held magnetic wand to deactivate stimulation (similar to VNS device wand)
(6) Implanted battery

F. Study Questionnaires

Quality of Life in Epilepsy (QoLIE-31)
Liverpool Seizure Severity Scale (LSSS)
Standard battery neuropsychological testing

G. Study Subjects

Entry criteria: Participants must be have diagnosed epilepsy that has failed at least three anti-seizure medications and have an identifiable epileptic focus (or foci) as confirmed by scalp EEG. Participants may continue AEDs while in the study.

Exclusion criteria: prior epilepsy surgery, age greater than 65 or less than 18, concurrent diagnoses that would prevent the participant from undergoing neurosurgery to place subdural electrodes and depth electrodes, participants who have not yet failed medical management, prior history of status epilepticus.

H. Recruitment of Subjects

Participants will be recruited from neurology and neurosurgery clinics at New York Presbyterian affiliated clinics and hospitals. After pilot studies, a proposed multicenter expansion to other major tertiary and quaternary care centers will be implemented.

I. Confidentiality of Study Data

All study data will be kept confidential following protocols endorsed by New York Presbyterian Hospital and its affiliates.

J. Potential Conflict of Interest

There is no identified conflict of interest.

K. Location of the Study

New York Presbyterian Hospital and its affiliates.

L. Potential Risks

Risks include those standard for any neurosurgical procedure involving general anesthesia. Electrodes will be placed stereotactically and carries the same risks as other neurosurgical procedures involving stereotactic placement of electrodes (e.g. those involved in DBS for movement disorders). Additional risks may include those associated with electrode failure, potential excess stimulation delivered and localized infections at the electrode implantation site and/or battery implantation site. Long-term risks are expected to be the same as or better than those associated with resection of brain tissue to remove seizure foci.

M. Potential Benefits

Patients who have failed antiepileptic therapies may see a reduction in their seizure number as well as an improvement in their overall quality of life and neurocognitive function in response to electrical stimulation.

N. Alternative Therapies

Neurosurgical resection of epileptogenic tissue. Vagal nerve stimulation. Bilateral anterior nucleus of the thalamus stimulation. Semi-closed loop (RNS) stimulation.

O. Compensation of Subjects

Subjects will have all medical procedures and clinic visits covered for the duration of the study.

P. Costs to Subjects

There will be no cost to the subjects.

Q. Minors as Research Subjects

There will be no minors used in this study.

R. Radiation or Radioactive Substances

No radiation or radioactive substances will be used.

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