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Title: Clinical Outcomes of deep brain stimulator electrodes placed using intraoperative computed tomography and frameless stereotaxis versus microelectrode recording and frame-based stereotaxis

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ABSTRACT

Background: Frame-based stereotaxis and microelectrode recording (MER) with mapping of target structures has been the gold standard for deep brain stimulator (DBS) implantation. Though supported by historical considerations, no Class I or II evidence exists that MER adds significant value to the DBS implant procedure. With the advent of advanced magnetic resonance imaging (MRI) and computed tomography (CT) imaging, particularly intra-operative imaging, the argument for the continued use of MER during DBS implantation has been substantially weakened. One rationale for pursuing CT-guided intraoperative imaging is due to presumed increase in patient comfort with this method. DBS implantation with MER requires that the patient remain awake during the entire procedure. MER with frame-based stereotaxis requires the patient to keep their head in a fixed position for a prolonged period of time during which time they remain awake, causing significant patient discomfort. Furthermore, Parkinson's disease patients must withhold their PD meds for a minimum of 12 hours prior to the procedure adding a sometimes significant degree of discomfort and anxiety to the procedure.

Objective: The goal of this study is to compare the clinical outcomes of DBS electrodes placed using intraoperative CT and frameless stereotaxis with those placed using MER and frame-based stereotaxis.

Design: The proposed study will be a prospective non-interventional data collection study.

Setting and Subjects: Subjects for this study will be idiopathic Parkinson's disease patients identified from the Oregon Health & Science University movement disorder clinic as candidates for deep brain stimulation therapy. We will also enroll patients referred by community neurologists to OHSU for deep brain stimulation therapy for idiopathic Parkinson's disease. These patients will be recruited in the OHSU movement disorder clinic during their evaluation for the deep brain stimulation procedure. Enrollment will continue until fifty subjects meeting inclusion and exclusion criteria have been implanted with electrodes using frameless stereotaxis and intraoperative CT. Data regarding quality of life, motor control, and amount of time during the day without levodopa-associated side effects will be collected pre-operatively and post-operatively. This data will be compared to historical controls who have been implanted with DBS electrodes using MER and frame-based stereotaxis. This data will be obtained from consulting the Veterans Affairs cooperative study entitled, "Bilateral Deep Brain Stimulation vs Best Medical Therapy for Patients with Advanced Parkinson Disease" published in JAMA in 2009 (5).

All surgical procedures will involve only Federal Drug Administration (FDA) approved stereotactic equipment, used in the manner for which they have been approved. All clinic procedures are standard of care for movement disorders patients in the deep brain stimulation program.

Intervention: This study will be a non-interventional data collection study.

Measurements: Data regarding patient age, diagnosis, intracranial target, complications, Unified Parkinson's Disease Rating Scale (UPDRS) Part 2 (activities of daily living), UPDRS Part 3 (motor examination), Parkinson's Disease Quality of life (PDQ-39), 3 day motor diary, and neuropsychological evaluation.

Analysis: The patients will be examined prior to DBS placement both on and off dopaminergic medications. All patients will receive their initial programming optimization visit approximately 30 days after electrode implant. The timing of further clinic visits for continued stimulator optimization will be up to the discretion of the DBS neurology provider and the patient. All patients will present for a 6 month visit following electrode placement. This visit will include the following procedures:

- UPDRS Part 2
- UPDRS Part 3
- PDQ-39
- Review of motor symptom diary
- neuropsychiatric evaluation, including:
    - Beck Depression Inventory-II (BDI-II)
    - Mattis Dementia Rating Scale-Second Edition (DRS-2)
    - Wechsler Abbreviated Scale of Intelligence (WASI)

We will also obtain information regarding adverse events directly related to surgery, falls and length of hospital stay.

A. Specific Aims

The objective is to compare the clinical outcomes of patients who receive placement of DBS electrodes by intraoperative CT scanning and frameless stereotaxis with those placed using frame-based stereotaxis and MER mapping for target verification The primary outcome measure is change in the motor section of the UPDRS in the OFF-levodopa state from pre-operative baseline to 6-month followup.

B. Background

Deep Brain Stimulation has become standard therapy for medically intractable Parkinson's disease, Essential Tremor, congenital and acquired dystonias, and is currently being investigated in the treatment of other common disorders. Class I evidence now supports its use in patients with advanced Parkinson's disease, in comparison to best medical therapy (1).

OHSU has been a pioneer in the development and use of DBS, and was the first center after Grenoble, France to perform DBS implantation. The original FDA Investigational Device Exemption studies supporting DBS were conducted at OHSU in 1990-91. Since then, OHSU was the first center to conduct a randomized prospective comparison study of subthalamic nucleus (STN) DBS v. globus Pallidus pars interna (GPi) DBS, the results of which have now largely been replicated in a multi-center protocol conducted by the US Department of Veterans Affairs and the National Institutes of Health (2).

Throughout the history of DBS implant procedures at OHSU, MER and mapping of target structures has been the gold standard. However, it is highly unlikely that *any* future study will ever provide Class I evidence that MER adds significant <u>value</u> to the DBS implant procedure (3). On the other hand, the best available evidence would indicate that MER does add <u>risk</u> to the DBS procedure; approximately 1% chance of hemorrhage per MER pass.

Prior to the routine use of advanced imaging in movement disorder surgery, MER provided the required degree of localization and verification of stereotactic target centers for movement disorder surgery. With the advent of advanced MRI and CT imaging, particularly intra-operative imaging, the argument for the continued use of MER during DBS implantation has been substantially weakened. (4)

In addition to the added risk of hemorrhage with MER there is also a presumed increase in discomfort for the patients during this procedure. With MER, the patient must remain awake for the entire procedure, including frame-placement, magnetic resonance imaging, surgical incision and drilling of the site of insertion, MER, and closure of the site. Patients must also withhold dopaminergic medications for a minimum of twelve hours prior to the procedure creating a significant degree of discomfort and anxiety.

With placement of DBS electrodes by intraoperative CT scanning and frameless stereotaxis, MRI is obtained prior to the procedure. The patient is then taken to the operating room for anesthesia, the head is placed in a frame, CT scan is obtained, pre-operative MRI and intra-operative CT images are merged, the navigation site is determined, and DBS is placed surgically.

Because the surgical targets have not changed, it is hypothesized that patient outcomes will be comparable to those seen using the traditional MER and frame-based surgery. Furthermore, it is believed that this procedure will prove to be the preferred technique both from a clinician stand point as well as the patient's as it addresses many concerns patients have regarding deep brain stimulation surgery.

C. Methods

1. Subjects

Fifty appropriate surgical candidates (Group 2), with Parkinson's disease implanted using an intraoperative CereTom 8-slice CT scanner (NeuroLogica Corporation, Danvers, MA), StealthStation® treatment guidance system, (Medtronic Surgical Navigation Technologies Minneapolis, MN), and using the NeXframe frameless system (Medtronic, Minneapolis, MN) will form the study group. Subjects will be identified through clinic visits and review of medical records. Informed consent will be conducted in person or through a recruitment cover letter for telephone consent. For telephone consenting, subjects will be given the opportunity to review the consent and discuss the study with the study team before they sign the consent or complete any study procedures. The information collected from these patients will be compared to the published data on 121 DBS patients who underwent implantation of electrodes via frame based stereotaxis and MER for the treatment of Parkinson's disease (Group 1). We will obtained de-identified data from theVA Cooperative study, "Bilateral Deep Brain Stimulation vs Best Medical Therapy for Patients With Advanced Parkinson Disease."(5) No medical records, source documents, or case report forms will need to be accessed to obtain the necessary values needed to compare the two groups. All procedures will involve only FDA approved stereotactic equipment, used in the manner for which they have been approved. Medtronic lead # 3387 will be used for all DBS implants.

a. Inclusion criteria

1. Idiopathic Parkinson's disease patients identified by OHSU movement disorders neurologists and community neurologists as deep brain stimulation surgical candidates who choose to undergo implantation of DBS electrodes using intraoperative computed tomography and frameless sterotaxis in the treatment of Parkinson's disease
    a. Hoehn and Yahr stage 2 or greater while not taking medication
    b. Responsive to levodopa

c. Persistent disabling symptoms (eg motor fluctuations, dyskinesia) despite medication
d. Experienced 3 or more hours per 24-hour period with poor motor function or symptom control

2. Surgical sites include subthalamic nucleus and globus Pallidus pars interna
3. Age > 18 years

b. Exclusion criteria

1. Subjects with atypical parkinsonism or parkinsons-plus syndrome
2. Subjects who have undergone implantation of DBS electrodes using MER and frame-based stereotaxis or computed tomography and frameless stereotaxis in the treatment of other movement disorders.
3. Other previous surgeries for Parkinson's disease
4. Age < 18 years
5. Surgical target site other than subthalamic nucleus or globus Pallidus pars interna
6. Subjects who choose to undergo MER and frame-based stereotaxis for the placement of electrodes.

2. Study procedures

As this is a non-interventional data collection study, we will obtain patient consent. We will then compare the study group of 50 patients with the historical cohorts in the following measures: UPDRS Parts 2, 3 and 4, change in PDQ-39, change in amount of time patient is experiencing Parkinson's Disease symptoms and/or side effects of treatment, and neuropsychiatric evaluation.
DBS settings will be optimized 30 (+/-3) days after electrode implantation. Further DBS programming optimization will be performed at 60 (+/-3) and 90 (+/-3) days post-implantation.

Studies	**Screening**	**Baseline**	**DBS Implant**	**30 day post-implant**	**60 day post-implant**	**90 day post-implant**	**6 month follow-up**
Informed consent	X						
Demographics	X						
History & Physical		X		X	X	X	X
UPDRS Part 2		X					X
UPDRS Part 3 (ON and OFF)		X					X
UPDRS Part 4		X					X
DBS programming				X	X	X	
PDQ-39		X					X
Motor Diary		X					X
Neuropsychiatric evaluation		X					X
Adverse Events			X	X	X	X	X
Medications		X	X	X	X	X	X

D. Data Analysis and Interpretation

(1) Experimental design.

The proposed study is a prospective data analysis to compare the clinical outcomes of DBS electrode placement using intraoperative CT and frameless stereotaxis versus an historical control of DBS electrode placement using MER with frame-based stereotaxis (5).

(2) Analysis.

The primary outcome will be a comparison of change in motor UPDRS (part 3) in the OFF medication/ON stimulation state at 6 months postoperatively between groups 1 and 2. Analysis will be based on the intent-to-treat principle. For patients without baseline data, follow-up data or both, the change score will be set to zero. The mean group change will be compared between treatment groups using a 2-sample t test.

Secondary outcomes will be a comparison between groups 1 and 2 in the change from baseline to 6 months in ON time without dyskinesia, PDQ-39, and UPDRS part 2. In addition, a comparison will be made between groups 1 and 2 in the change from baseline to 6 months in the Beck Depression Inventory-II (BDI-II), Mattis Dementia Rating Scale-Second Edition (DRS-2), and the Wechsler Abbreviated Scale of Intelligence (WASI) , using a 2-sample t test. The sample size and power calculations are 2-tailed with an α level of 0.05.

(3) Sample Size Calculations.

Data from historical control patients using MER and frame-based stereotaxy (5) will be compared with 50 patients who undergo DBS placement using frameless stereotaxis and intraoperative CT.

E. Human Subjects

1. *Risks to Subjects*: As this is a non-interventional data collection study, no additional risks will be posed to the patients involved in this study. The patients will be treated using accepted surgical techniques, such as planning and surgical execution and all steps will be carried out in the usual fashion of performing such procedures in the Department of Neurological Surgery at OHSU. All clinical outcome measures are standard of care in the movement disorders center for patients in the deep brain stimulation program. Patient confidentiality will be respected during information retrieval.

2. *Potential Benefits of the Proposed Research to the Subjects and Others*: This research project proposed here aims to drive a paradigm shift, from MER verification of stereotactic targets, to an entirely image-based anatomic targeting methodology. We would like to demonstrate non-inferiority of the image-based anatomic targeting method in terms of treatment of Parkinson's disease symptoms.

   The implications of this shift are:
   A. Increased patient comfort
   B. Operative procedures will be faster.
   C. Operative procedures will be easier, absent the requirement for MER equipment, macroelectrodes and electrophysiologic expertise.
   D. Most operative procedures can be performed entirely under general anesthesia.
   E. If intraoperative imaging is used, anatomic verification of the electrode position can be established prior to the patient leaving the operating room.
   F. Intraoperative images are provided to the neurologist which can be used to help guide selection of optimal programming configurations.

3. *Importance of Knowledge to be Gained*: We project that this paradigm shift will simplify and enhance the patient experience, which will promote the use of DBS technology for an expanding list of indications and applications. Data collected and shared with neurosurgical colleagues will provide increased knowledge regarding accuracy of functional stereotactic procedures and help to improve outcome.

F. References

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