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High Frequency Oscillation in Pediatric Epilepsy Surgery

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Introduction:

Intra-operative electrocorticography (ECoG), based on interictal spike and spike patterns, is performed to optimize delineation of the epileptogenic tissue in the operating room during epilepsy surgery. Similarly, extra-operative electrocorticography is often recorded over days to weeks with intracranial grids and depth electrodes, when the epileptogenic zone is not clearly localized with non-invasive studies and/or with intra-operative ECoG. Surgical resection following extra-operative ECoG is then "tailored' by the seizure onset zone as the gold standard. High frequency oscillations have been identified as a more precise biomarker for epileptogenic tissue. The aim of the study is to determine prospectively if ECoG- tailored surgery combining HFOs and standard clinical resection with ECoG, compared to standard clinical resection with ECoG alone, is feasible and will lead to an equal or better seizure outcome; the comparison to HFO + ECoG, versus ECoG alone, could be either in the form of interictal spikes on intra-operative ECoG or seizure onset zone on extra-operative ECoG.

Background and Rationale:

Epilepsy occurs in 0.5-0.7% of the population, of which 25% are children. About 30% of subjects with focal epilepsy do not respond well to medication, and half of them are eligible for epilepsy surgery. In recent years, the importance of early epilepsy surgery has been stressed, as successful surgery may lead to seizure- and medication-freedom and improved social and cognitive development, especially in children. The current rate of seizure freedom following epilepsy surgery is around 65%. During surgery, in most medical centers, either intra-operative ECoG is recorded to identify the irritative zone, defined by the spatial distribution of interictal spikes, or extra-operative ECoG is recorded to identify the seizure onset zone. The presence of epileptiform brain activity/spikes, or the seizure onset zone, identified by clinical neurophysiologists, is used to guide the neurosurgeon with respect to the boundaries of brain tissue that is necessary for resection to achieve seizure freedom. Spikes are considered biomarkers of the presence of epilepsy, and seizure onset zone indicates where the seizures may be generated. Neither spikes nor seizure onset zones accurately identify the location and the extent of the epileptogenic zone, defined as the cortical tissue whose complete removal is necessary to achieve post-operative seizure freedom.

High frequency oscillations (HFOs, 80-500 Hz) on ECoG have recently been identified as a new biomarker for epileptogenic tissue. Retrospective observational research, as well as more recent prospective observational studies, show that HFO presence strongly relates to, and may predict more accurately, the epileptogenic zone, and that the resection of brain tissue containing HFO may be superior than resection of brain tissue containing spikes and seizure onset zone in rendering patients seizure-free. The area showing HFOs usually overlaps with, but may be smaller than, the area with spikes

and seizure onset, and HFOs do not tend to propagate to distant sites as spikes and seizures do.

Standard Clinical Practice

During surgery, current clinical practice is to measure epileptic activity that we call epileptic spikes (on intra-operative ECoG) or seizure onset zone (extra-operative ECoG) with EEG recordings. Current clinical standard of practice in either intra-operative ECoG or extra-operative ECoG is recorded to identify epileptic zone and seizure onset zone. The presence of epileptiform brain activity/spikes, or the seizure onset zone, identified by clinical neurophysiologists, is used to guide the neurosurgeon with respect to the boundaries of brain tissue that is necessary for resection to achieve seizure freedom. The particular part of the brain that has either of these abnormalities, is removed. We have used this method for over 40 years.

New Research HFO Method

Recently, it has been discovered that we can also measure other epileptic activity, High Frequency Oscillations or HFOs, by recording EEGs at a higher frequency rate. These HFOs on the EEG recordings appear to point out the epileptic brain tissue better than epileptic spikes or seizure onset zone.

In this study we will compare the two groups of patients to see what works best: standard clinical practice only, or standard clinical practice along with HFOs. The results of this study may change the way we operate on epilepsy surgery patients in the future.

Hypothesis: We hypothesize that the strategy of incorporating HFO data to a standard ECoG-guided resection in pediatric epilepsy surgery will result in improved postoperative seizure outcome than the traditional approach.

Objective:

The primary objective is to determine if HFO data in addition to ECoG data (experimental group, arm 1), compared to standard ECoG data alone (current standard control group, arm 2), will lead to improved post-surgical seizure outcome 1 year after surgery.

Secondary objectives include the comparison of incidence of neurologic deficits, neuropsychological outcomes (when available with clinical testing), and quality of life outcomes.

Study Design and Procedures:

A single-blinded randomized control trial including subjects with refractory focal epilepsy who undergo surgery with intra- or extra-operative electrocorticography. Surgery is

tailored by HFOs and standard ECoG interpretation (spikes on intra-operative ECoG or seizure onset on extra-operative ECoG) (arm 1), or tailored by standard ECoG alone (arm 2).

Randomization
Informed consent will be obtained 1 to 7 days to up to 3 months prior to the day of surgery. Prior to surgery, the subject will be randomized into the cohort arm in a 1:1 ratio.

Blinding
Blinding of the clinical neurophysiologists and neurosurgeons for treatment allocation is not feasible because of the character of the intervention. Therefore, this is a single-blinded trial as subjects will be blinded to the cohort arm to minimize bias of the follow-up results. The treating neurologist, if other than the clinical neurophysiologists in this study, will remain blinded.

Number of Subjects:
30

Inclusion Criteria:

- Age 0-21
- Refractory focal epilepsy
- Planned resective epilepsy neurosurgery with ECoG, with the goal of tailoring the resection

Exclusion Criteria:

- Subjects undergoing non-resective neurosurgery

Recruitment of Subjects:
Subjects with refractory epilepsy undergoing epilepsy surgery with ECoG to guide the extent of the resection.

Length of Study Visits and detail:

This research study will not require any additional time in the hospital after surgery. However, will be following the subject for epilepsy outcome up to 12 months after surgery.

Chart review of clinical records such as neurological, MRI, EEG and other clinically relevant information pertaining to the outcome of surgery will be collected.

Subjects or their caregivers will be asked to fill out questionnaires about seizure frequency, medication and day to day function in various life areas at each visit with the neurosurgeon/neurologist.

Schedule of events below:

PRE-SURGERY	**SURGERY**	**POST-SURGERY**				
Visit 1 /Baseline		**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
0 day-3 months prior to surgery		1-7 days after surgery	3 months	6 months	9 months	12 months

Pre-Surgery

- Consent
- Neurosurgeon visit
- Baseline Questionnaire

Post-Surgery (at every visit)

- Neurosurgery/Neurology Visit
- Follow-up Questionnaires

Questionnaires will take about 30 minutes to complete. We may send the questionnaires home a week prior to a return visit to alleviate time at the doctor's office.

Questionnaires

NIH Pediatric Stroke Scale
Child Behavior Check List
Quality of Life in Epilepsy (Adults)
Quality of Life in Childhood Epilepsy

Procedure Detail:

Intra-operative ECoG, which could be pre-resection, post-resection, or both, during brain surgery would be determined based on clinical decisions. Similarly, extra-operative ECoG would also be determined based on clinical decisions, and would be pre-resection.

For those subjects randomized to the standard clinical care with ECoG only (control arm), ECoG would be recorded but not assessed for HFO until after the clinical decision has been made with respect to site and margin of the resection. Only cortical areas deemed abnormal by standard clinical ECoG would be resected.

For those subjects randomized to the HFO + standard clinical care with ECoG combined (experimental arm), ECoG would be recorded AND assessed for HFO rapidly in the operating room (within 10 minutes) to minimize patient risk and while the neurosurgeon begins the initial resection. Should HFO persist after resection, further resection to ensure complete removal of HFO and standard clinical ECoG abnormalities may be possible. Cortical areas generating HFO and/or abnormal by standard clinical ECoG would be resected, with the exception of HFO-only presence in eloquent cortex, which would be spared. Eloquent cortex is defined as sensorimotor cortex, primary language cortex (Wernicke's and Broca's areas), and primary visual cortex.

Benefits of Study:
HFO analysis could determine/predict a better surgical outcome.

Potential Risks:

In epilepsy surgery there are always risks.
1. The patient may not become seizure free.
2. The patient may lose or may damage an area that is close to important function such as motor or speech functions.
3. The patient may develop a surgical complication such as infection, hydrocephalus or stroke.

In Standard Surgery plus HFO Method Risk: Additional risk may be unexpected neurologic deficit.

There will be every effort made to minimize loss of major brain function, such as language, motor skills, sensation, and vision, to what may be already anticipated from the standard clinical care approach. Should any of these 4 major brain function areas be found to have HFOs only, and not on standard ECoG analysis, these important areas of brain function will not be resected.

The likelihood of longer anesthesia time is very low since HFO analysis will begin before or concurrently with standard method. Therefore we do not expect any additional time under anesthesia for either method.

There is no additional risk of recording HFOs at higher frequencies. Higher frequency simply allows us to capture brain signals at higher frequency rate.

Randomization: There is no risk or benefit from randomization given that standard of care ECoG will be completed during surgery.

Questionnaires: There are no risks to these questionnaires other than the inconvenience of the time involved in answering the questions.

Potential risks include loss of confidentiality. To protect you from this risk, all electronic study data will be kept in a password-protected, encrypted database. Other study related materials that include personal health information will be kept in a secure area accessible only by study personnel.

Where will data be stored?

Data will be stored in an encrypted database which is password protected. Only study personnel will have access to the data. EEGs data done at UCLA, for data analysis will be de-identified. This information will be stored in a secure area accessible to authorized personnel only and data will be kept for future studies and or publication.