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Final IRB Proposal-CRC Rotation

Duration of Treatment With Levetiracetam in Late Onset Post-Stroke Seizures

1. Introduction

Stroke is a leading cause of seizures in the over-35-year-old age group (accounting for approximately 11% of etiologies). Stroke represents as much as half of seizure etiology in the elderly, and the incidence of seizures increase by 30-40 fold with age greater than 60.

"Early" seizures occur less than 2 weeks within a cerebrovascular insult and are thought to be caused by disturbances in cell membranes and neurotransmitter imbalances from acute injury to brain parenchyma. "Late onset" post stroke seizures occur after 2 weeks following the initial insult and are thought to be secondary to hyperexcitability from gliosis; the frequency of recurrent seizures in patients with late onset seizures following stroke vary in the literature between 3 and 66%[1][2]. Patients with hemorrhagic strokes, cortical stroke location, and high stroke severity are at greater risk for seizure overall, while late-onset seizures following strokes have been shown to be an independent risk factor in epilepsy following ischemic stroke[3]. The current practice at our institution for patients with post-stroke late-onset seizures is to treat with anti-epileptic therapy for 6 months but it there is no standard of care in nation-wide clinical practice.

Seizures are costly as they result in high rates of hospitalization, pose risks of respiratory compromise (i.e. aspiration) and potential public health risks. However, there is a lack of data in the literature examining any benefit of any particular treatment duration over another in this patient population and it is unclear whether AEDs affect patient outcomes[4][5]. Moreover, while many drugs are available for the treatment of seizures, many have significant side effect profiles (i.e. phenytoin, carbamazepine, lamotrigine) and some do not have well established long-term side effect profiles (levetiracetam, zonisamide). All of these factors come into play, in addition, given the disparity of recurrence rates, when attempting to prevent seizure recurrence in this particular population.

While neocortical hyper-excitability has been described in the months following transient brain ischemia in animal models[6], we propose that there is a period of time of several months after which brain tissue self-modulates and reduces the amount of gliosis in a particular injured area. The hypothesis of this study is that duration of treatment with anti-epileptics beyond that of the typical duration of treatment at our medical center does not significantly affect the rate of seizure control in patients with late-onset post-stroke seizures. Our hope is to identify a sufficient treatment period which will prove effective in achieving a trade-off between reducing seizure occurrence and minimizing AED adverse effects.

2. Study Design and Statistical Procedures.

A. Study Design

This will be a prospective, interventional, randomized clinical trial run at multiple medical centers (based on the sample size calculations mentioned elsewhere). The study population

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[1] Camilo O , Goldstein L. Seizure and Epilepsy after Ischemic Stroke. Stroke. May 2004
[2] Burn et al. Epileptic Seizures after a first stroke: the Oxfordshire community stroke project
[3] Bladin et al. Seizures After Stroke: A prospective Multicenter Study. Archives of Neurology Nov 2000
[4] Camilo O , Goldstein L. Seizure and Epilepsy after Ischemic Stroke. Stroke. May 2004
[5] Kwan J, Wood E. Antiepileptic drugs for the primary and secondary prevention of seizures after stroke. Cochrane Database of Systematic Reviews. 2010, Issue 1.
[6] Stroemer RP et al. Neocortical neural sprouting, synaptogenesis, and behavioral recovery after neocortical infarction in rats. Stroke, 1995.

will include patients with acute stroke, age > 18, at least one seizure occurring after 2 weeks after the patient's initial stroke. Attempts at recruiting patients as close to the first date will be made by recruiting efforts being primarily directed towards inpatient services. Due to its relatively well-tolerated side effect profile and efficacy in controlling late-onset post-stroke seizures[7], levetiracetam will be used as anti-epileptic treatment.

All patients enrolled in the study will be treated with levetiracetam for 6 months, after which half of the patients will be randomized to an extended-treatment arm (to receive 6 additional months of levetiracetam) vs. limited-treatment arm (to receive no additional months of levetiracetam). Patients will be followed for 6 months or until they reach a composite endpoint of seizure, mortality or stroke, whichever comes first. A rate of attaining the composite endpoint will be calculated based on the total number of subjects reaching the composite endpoint divided by the total number of subjects in the arm at the end of the study.

At the study entrance, patients will receive stroke & seizure workup (EEG, MRI of brain with T2, FLAIR, DWI, ADC sequences and MRA brain with either MRA neck, or CT head without contrast with carotid Doppler for patients that are unsuitable for MR, HbA1c, TTE). Patients will be followed with regular visits to neurology clinic every 3 weeks to assess for seizure control and adjust levetiracetam dosages. Serum levetiracetam levels and levetiracetam dosage will be obtained and recorded at each followup visit. Modified Rankin scale, VA Cooperative Seizure Score will be obtained at 6 and 12 months to assess for .

B. Statistical Procedures

Power Analysis

Based on descriptions from Kutlu et al. the recurrent seizure incidence in patients with late post-stroke seizures at 1 year follow up on levetiracetam therapy is estimated at approximately 17%. The risk of seizure recurrence after a late onset seizure in the post-stroke setting without therapy varies widely in the literature, however, and this is further complicated by inconsistent study designs, inclusion of both early and late stroke population together, and varied follow up times. Based on discussions with faculty at CUMC, and considering the potential adverse events of levetiracetam (a relatively new medication whose long-term side effect profile has not been fully studied), an effect size of approximately 8% was considered clinically significant. Using a chi-squared test between two groups, the sample size for the study with an effect size of 8% using beta of 0.2 and alpha of 0.05 is **430** patients using a power of 80% and an alpha of 0.05.

It is important to note that further data on seizure frequency in this patient population and adverse effects of Keppra are awaited to inform the decision of which particular incidence at which to estimate seizure frequency in this population. For example, it is possible that the clinically significant effect size may potentially be as high as 15% in the case of higher seizure rates in the population, or potential adverse effects of levetiracetam. In this case, using a chi-squared test between two groups, the sample size for the study would be 141 patients. Given the lack of data, however, a more conservative effect size of 8% will be used.

Statistical Calculations

1) A chi-squared statistic will be computed using the rate of population reaching the endpoint rates from both arms.
2) Outcome analysis (time to composite endpoint) will be obtained by Kaplan Meier analysis.
3) A multivariable regression analysis will be performed using a Cox proportional hazards model will be performed for primary time to composite endpoint using the variables:
    a. hemorrhagic stroke
    b. stroke severity as measured by NIHSS
    c. Cortical stroke location

[7] Belcastro et al. Levetiracetam in newly diagnosed late-onset post-stroke seizures: A prospective observational study. Epilepsy Research.

d. Time to seizure onset

(a.-c. have been described in the literature as being risks for seizure overall).

Descriptive statistics will be used to collect the following data points at study entrance:

- Age
- Gender
- Ethnic group
- Time to onset of first seizure net of 2 weeks post-stroke
- Presence of early seizures (ES)
- Location of stroke
  - Cortical
  - Non-cortical
- NIH Stroke Scale
- History of >1 stroke (ischemic/hemorrhagic) prior to current stroke
- Etiology
  - Ischemic: embolic, thrombotic, unknown
  - Hemorrhagic: amyloid, vasculitis, lacunar, AVM, unknown
- Family history of seizures (1st - 2nd degree relative)

3. Study Procedures

N/A

4. Study Drugs or Devices

Levetiracetam as above.

5. Study Questionnaires

VA Epilepsy Cooperative Seizure Assessment

- combines frequency and severity in a weighted scoring system for simple and complex partial and generalized tonic-clonic seizures

Modified Rankin Scale

NIH Stroke Scale (administered at study entrance)

6. Study Subjects

Based on previously noted power analysis, a total of 860 patients will be enrolled, with 430 in each arm.

Inclusion criteria

- Patients >18 yo
- Acute stroke
  - The diagnosis of acute stroke will be made based on clinical assessment and neuroimaging.
- Presence of at least one late onset seizure (>2 weeks)
  - The diagnosis of seizure will be made by a neurologist or epileptologist on clinical grounds in combination with EEG.

Exclusion criteria

- Acute brainstem/deep nuclei stroke
- Inability to tolerate medication
- Inability to control seizure with dose of 3000 mg/day of medication
- History of prior treatment with anti-epileptic, including for current episode of seizure
- History of prior seizure / epilepsy
- Alcohol, opiate, or benzodiazepine abuse in the month prior to study enrollment
- Stroke symptoms and no evidence of structural lesion on imaging

7. Recruitment

Patients will be recruited via emails to Neurology department attending physician listservs, particular epilepsy, neurological ICU and stroke services, at each academic center informing personnel about the study and study coordinator contact information. Bulletin board advertisements will be placed in communal areas and in neurology clinics with same data.

Patients will be recruited using informed consent procedure by either the principal investigator or the study coordinator(s). Case will be discussed with the attending physician in the hospital or the clinic prior to approaching the patient. If patients are not able to be consented, next of kin, health care proxy, or power of attorney will be approached and consented.

8. Confidentiality of Study Data

All patient data will be placed into a secure, password protected Microsoft Access database on a local server accessible only to Neurology departmental personnel. Each patient record in the database will be assigned a numerical identifier instead of first name and last name. Access will be restricted to the principal investigator and the study coordinator. Following the last day of clinical information input, the database will be locked from editing.

9. Potential Risks

While levetiracetam is a relatively well tolerated AED, its side effect profile is notable for paradoxical increased aggression and agitation, which has been described in up to 10% of patients. Moreover, it is a relatively new medication, which means that its long-term adverse effects have not been adequately studied in seizure and epilepsy patients. Therefore, a number of long-term risks of the medication remain unknown at this time.

10. Potential Benefits

As stated before, the risk of recurrence of seizures in the levetiracetam group in one previous study was measured at close to 15%. The potential benefits, provided this is a negative study, would be to identify a time period of treatment with AEDs which would minimize negative outcomes following late onset seizures in stroke while minimizing the existing and yet unknown effects of levetiracetam. In the case of a positive study, multivariate analysis could delineate several risk factors for reaching the composite endpoint that may clue us into the underlying reasons behind the variability in the clinical data on recurrence of seizures in this particular population.

11. Alternatives

Patients may choose to not to participate in this study on the grounds that they do not want to run the risk of a recurrent seizure while off medication. They may also choose to try another medication to prevent seizures if they desire but will not be able to participate in this study. Gabapentin has been evaluated in this population. Alvarez-Sabin et al. showed in a prospective study of gabapentin in late-onset post-stroke seizures that patients developed recurrent seizures in 18.3% of cases[8] during a mean follow up time of 30 months. However, the sedating and other various effects of gabapentin are much more prevalent than that of levetiracetam.

[8] Alvarez-Sabin et al. Gabapentin in late-onset poststroke seizures. Neurology, 2002.