Title: Seizure Prophylaxis in Aneurysm Repair (SPAR)

Principal Investigators:

Cormac Maher, MD, B. Gregory Thompson, MD, Aditya Pandey, MD

OVERVIEW

Research Objectives:

To examine the utility of levetiracetam (UCB Pharma, Brussels, Belgium) for seizure prophylaxis in patients undergoing surgical repair of ruptured and unruptured intracranial aneurysms.

Hypothesis:

No difference exists in seizure frequency post-aneurysm treatment between the levetiracetam and no levetiracetam groups.

Background information and Rationale:

Seizures are a potential complication of surgical repair of intracranial aneurysms. In order to prevent seizures, many surgeons administer prophylactic anti-epileptic medications during the intra-operative and post-operative period; however, such practice is not supported by clinical data [Raper et al]. A recent retrospective review found that the incidence of postoperative seizures following intracranial aneurysm surgery was actually higher in those who received anti-epileptics versus those who did not [Raper et al.]. Given the retrospective nature of this study, it

is not certain that both groups were equally at risk for seizures. Older retrospective studies have also suggested that antiepileptic prophylaxis confers no benefit [Sbeih et al., Rhoney et al.]. Recent information on patients undergoing surgery for supratentorial brain tumors has also cast some doubt on the efficacy of seizure prophylaxis. A recent trial randomized 123 patients undergoing craniotomy for resection of supratentorial tumors to either perioperative seizure prophylaxis with phenytoin or no seizure prophylaxis [Lang et al]. These investigators found that prophylactic use of anti-epileptic medication did not reduce the risk of perioperative seizures and was associated with an increased risk of adverse events. They suggested that the routine use of prophylactic anti-epileptic medications in that population may not be indicated.

The strongest argument in favor of routine use of anti-epiletic medications for patients undergoing craniotomy comes from older retrospective reviews that have suggested that rates of post-operative seizures decreased compared with historical controls following the implementation of prophylaxis [Ohman et al., Bidzinski et al.].

In 2009, an expert panel convened by the Stroke Council of the American Heart Association recommended against routine use of prophylactic anti-epileptic medication for patients with ruptured intracranial aneurysms due to lack of proven benefit [Bederson et al]. Although this group did not make any recommendations regarding the use of prophylactic anti-epileptic drugs during the surgical treatment of unruptured aneurysms, the risk of seizures, and therefore the potential benefits of seizure prophylaxis, appears to be lower in these patients compared with those with ruptured intracranial aneurysms Bederson et al., Baker et al]. Despite a lack of evidence for the use of anti-epileptic medication in preventing seizures in patients undergoing

microsurgical treatment of ruptured and unruptured brain aneurysms, the use of these medications remains common at many institutions including UMHS.

After a thorough review of the existing literature as well as a review of our own practice, the investigators have concluded that the decision to treat patients undergoing aneurysm repair with levetiracetam has reached true clinical equipoise. In other words, we cannot favor a decision to either administer or not administer this drug in these patients based on the existing information. The utility of anti-epileptic prophlaxis in the perioperative period for patients undergoing intracranial aneurysm repair remains a common practice that is not supported by the current literature that includes retrospective analyses as well as prospective trials for similar but not identical types of patients. We propose to settle this dilemma by performing a prospective randomized trial in patients undergoing aneurysm repair in order to definitively determine if the common practice of perioperative antiepileptic drug administration has any utility.

We have chosen to use levitiracetam as the medication for seizure prophylaxis for those patients who will randomize to perioperative seizure prophylaxis. Although phenytoin was the most common drug used for perioperative anti-seizure prophylaxis for many years, it has now been replaced by levetiracetam at many centers because of a perception that it is easier to administer and has fewer side effects [Zachenhofer et al, Milligan et al, Szaflarski et al., Lim et al]. The use of levetiracetam rather than phenytoin will reflect the practice pattern of most centers across the United States.

METHODS

Timeline: Prospective data for subjects will be collected on a secure file with password access for until up to 10 years after all data is published.

Inclusion/Exclusion criteria:

Inclusion:

1. Adult (≥18 years)
2. Presence of intracranial aneurysm (with or without rupture)
3. Patients with unruptured aneurysms must be recommended for microsurgery. Patients with ruptured aneurysms should be recommended for clipping or coiling.

Exclusion:

1. History of seizures within last 10 years
2. History of epilepsy
3. History of prior stroke
4. Currently prescribed medication with anti-epileptic activity (keppra, dilantin, tegretol, lamictal, topamax, etc.)
5. Brain tumor
6. Pregnant or nursing woman
7. Known levetiracetam allergy

Recruitment:

All patients seen at the University of Michigan Health System that meet inclusion criteria are currently seen by one of the investigators for routine clinical care. Prior to surgery, the study

will be explained to potential subjects and/or their legally authorized representatives by an investigator or a qualified study team member and they will be able to ask any questions that they may have. In addition, they may contact the PI (by phone, email, or mail). The investigators will recruit from their own patient population. No additional patient recruitment will be pursued.

Design:

Patients that meet all eligibility criteria will be randomized to either a "levetiracetam" or "no levetiracetam" group. There will be no attempt to "blind" the patient or caregivers with respect to group assignment. The group assignment will be known to the patient as well as relevant caregivers.

Patients in both groups will be treated according to all current reasonable clinical practices for the surgical treatment of intracranial aneurysms and its postoperative care. With the single exception of prophylactic levetiracetam administration to only one group, there will be no differences by design between the two groups with respect to treatment.

Those assigned to the "levetiracetam" group will receive a 500 mg intravenous dose during the operative case and then will be maintained on 500 mg orally twice a day for a total of seven days Those patients that are assigned to the "no levetiracetam" group will receive no levetiracetam or any other anti-epileptic medications unless the treating physicians determine that such medications are clinically indicated based on specific circumstances. The use of any anti-epileptic medications will be recorded.

As is typical for all patients undergoing craniotomy for aneurysm repair, patients will be monitored in the neurological intensive care unit for at least one day following surgery. The

patients may then be transferred to a ward room where they will continue to be monitored according to standard clinical practices. If a subject is discharged prior to 7 days, periodic chart review and examination at routine clinical follow ups will be used to determine occurrence of seizure. If a seizure occurs in any patient, the seizure will be treated according to best clinical practices as determined by the treatment team without any regard to the patient's group assignment in the study.

A dataset will be prospectively assembled on each patient included in the study. Recorded information will include patient age, gender, location of aneurysm, size of aneurysm, duration of surgery, surgeon's assessment of degree of brain retraction during surgery (on a 3 point scale: less than average, average, more than average), the surgeon's degree of cortical damage during surgery (on a 3 point scale: less than average, average, more than average), the occurrence of an intraoperative hemorrhage, the occurrence of any other unexpected intraoperative events, the dose of levetiracetam and the duration of administration, any side effects or possible side effects of levetiracetam, the dose and duration of administration of any other anti-epileptic medications, the occurrence of any seizures including the number of such events, their duration, their treatment, and their sequelae if any.

Assessments will occur at routine care follow-up visits. These visits typically occur at 1-2 months, 4-6 months, and 6-12 months and up until 5 years +/- 6 months after surgery. Clinical data collected at these visits, specifically, the incidence of seizures, will be used for the study. Additionally, the study team may follow up on any previously reported adverse events.

The final assessment of clinical outcome will be made at the time of the regularly scheduled post-surgical outpatient appointments with the surgeon. At that time, the patient data will be de-

identified and entered into the registry. The study team will contact the patient via the telephone to try to obtain their 5-year clinical status.

The patient may be withdrawn from the study at any time if the treating physician or patient does not believe it is in the patient's best interest to continue to participate. All such instances will be recorded.

INFORMED CONSENT

When patients are seen in their physician's clinic for standard clinical care, the study will be explained to them by their physician (a study team investigator) or another qualified study team member and they will be able to ask any questions that they may have. In addition, they may contact the PI (by phone, email, or mail). Patients with ruptured aneurysms will be seen by a study investigator and informed consent may be obtained by an investigator or other qualified study team member.

An attempt will be made by the study team to contact previous participants via telephone to obtain their health status. In this case, a comprehensive telephone consent will be used to collect this information and the interaction will be recorded and maintained in the subject's study record.

PROCEDURES FOR MAINTAINING CONFIDENTIALITY

Data Security: Subjects will be given an ID number after being enrolled in the trial. Their ID number will be used on their data collection sheets. A linkage file will be maintained with patient identifiers to enable the study team to conduct chart reviews to extract data and monitor adverse events. Patient information will be de-identified prior to entry into the database. The database will be password-protected. The linkage file will be maintained in a secure, electronic database

for ten years following the close of the study. At that time, patient identifiers other than study ID will be destroyed.

ASSESSMENT OF RISKS AND BENEFITS

Risks:

Levetiracetam will not be given to half of the study subjects. Although levetiracetam is often used in these patients for seizure prophylaxis, its utility has never been established. A recent randomized trial found that prophylactic administration of antiepileptic medications in those undergoing routine craniotomy for tumor did not reduce the risk of seizures in that population. Therefore levetiracetam administration should not be considered standard treatment and withholding this medication falls within the scope of reasonable clinical practice.

Levitiracetam is associated with side effects in some cases. A recent trial of levitiracetam prophylaxis found that 1 patient had an adverse drug reaction out of 105 patients that were treated with this drug in the perioperative period [Milligan et al].

As with most anti-epileptic medications, levetiracetam appears to have some teratogenic potential. This potential appears to be dose dependent. All women of child-bearing age will undergo pregnancy testing prior to treatment per UMHS routine care practices. Pregnant women will be excluded from this study and will be treated according to standard practices of the treating physician.

There is a risk of loss of confidentiality. This risk is considered minimal and will be reduced by the maintenance of only de-identified data sets on password protected files.

Benefits: Participating subjects may benefit from increased monitoring by the study team as participants in the trial. Subjects in the levetiracetam group may benefit from reduced incidence of seizure. Subjects in the no levetiracetam group may benefit from a reduced indicence of side effects. Additionally, the study will yield important information to the community of physicians and researchers, and ultimately their patients; thus, there will be benefits to society.

ANALYSIS OF DATA

The two groups will be compared to verify that no significant differences in group composition were present. The treatment and no treatment groups will then be compared with respect to the occurrence of seizures including their frequency and duration. The treatment and no treatment groups will be compared with respect to the occurrence of levetiracetam side effects or possible side effects. Significance will be determined at $p<0.05$.

Up to 100 subjects will be recruited for this study. An interim analysis maybe conducted at any time during this study.

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