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Title: A shortened antiepileptic drug (AED) course in surgical brain tumor patients: a randomized trial

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IRB Protocol

Title: A shortened antiepileptic drug (AED) course in surgical brain tumor patients: a randomized trial

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Abstract: Seizures are one of the leading neurologic complications in brain tumor patients. This has led neurosurgeons to use antiepileptic drugs (AEDs) as prophylaxis. However, the drugs are often not withdrawn right away and patients are referred to oncologists for follow-up care. Neither specialty has particular expertise dealing with antiepileptic drugs and as a result, there has been no standardized protocol used to discontinue the drugs and many patients stay on them indefinitely. The result has been considerable practice variation in regard to the use and length of AEDs in the post-operative period[2]. The American Academy of Neurology (AAN) guidelines recommend the discontinuation of Antiepileptic Drugs (AEDs) after the first post-operative week in patients without seizures[1]. In an attempt to develop Neurosurgery clinical guidelines for AED use in post-operative brain tumor patients, we will evaluate two different courses of levetiracetam.

Patients who have had a surgical resection of a brain tumor will be randomized to levetiracetam for one week or for six weeks. The primary study endpoint will be performance on a validated neurotoxicity scoring system at 6 weeks post-op. We hypothesize that patients on a shortened AED course (1 week) will have less neurotoxicity as measured by a validated neurotoxicity scoring instrument compared to patients on 6 weeks of treatment. Secondary endpoints will include number of seizures and adverse events. We will also measure medication adherence, and mood alterations to determine if these have any correlation with AEDs.

Background: Up to 35% of patients undergoing craniotomy for non-acute traumatic pathology experience post-operative seizures within the first week[1]. A recent Cochrane database systemic review by Pulman *et al*. reviewed six randomized control trials that aimed to determine the efficacy and safety of prophylactic AED use in patients undergoing craniotomy for non-traumatic pathology. Only one trial reported a significant difference in early seizure outcomes between patients on prophylactic AEDs and control patients[2]. The authors concluded that evidence is limited to suggest prophylactic AEDs are effective in preventing post-operative seizures. This systematic review included patients with non-traumatic pathology rather than with brain tumors alone, who may be at further increased seizure risk compared to other non-traumatic pathologies.

Prophylactic use of AEDs for patients undergoing craniotomy for brain tumors is common practice, and in a recent survey conducted by Glantz et al., 81% of practicing neurosurgeons reported that they prescribed prophylactic AEDs post operatively to patients without a history of seizures[3]. However, there are no clear clinical guidelines to support this practice, raising the question of whether prophylactic AEDs improve seizure incidence or subject patients to unnecessary medication side effects. Ansari *et al.* performed a retrospective analysis of seizure occurrence with and without post-operative AED prophylaxis over a six-year period and found no statistically significant benefit to prophylactic post-operative AEDs for intra-axial tumors[4]. Additionally, their study observed a trend (not statistically significant) of higher seizure incidence in patients receiving prophylactic AED therapy. Garbossa *et al*. performed a retrospective two-center cohort study of AED prophylaxis in surgically treated high-grade gliomas to assess effectiveness of perioperative AED use[5]. They reported that AED use does not provide substantial benefit. Wu *et al.* performed a prospective randomized clinical trial of phenytoin for perioperative seizure prophylaxis in patients with intra-axial tumors[6]. They found no benefit from AED use and increased adverse events post-operatively with AED use. Additionally, their study found a low overall incidence of post-operative seizures. Therefore, the traditional factors that are felt to increase seizure risk such as intra-axial tumors, cerebral edema, etc., have not been found to justify the routine use of AEDs in surgical brain tumor patients.

Hypothesis: We hypothesize that patients on a shortened AED course (1 week) will have less neurotoxicity as measured by a validated neurotoxicity scoring instrument compared to the patients on 6 weeks of keppra.

Primary Objective: To determine the difference in patient reported neurotoxicity associated with a shortened course (1 week) of levetiracetam compared to a longer course (6 weeks).

Secondary Objectives: To determine if seizure rates, medication adherence and mood alterations correlated with a shortened or longer course of levetiracetam.

Patient selection criteria:

Inclusion criteria –

- Adult (>18 years of age and older) patients who have or will have undergone surgical resection or biopsy of a supratentorial brain tumor and are able to consent for themselves. During the informed consent process subjects with perceived cognitive disability will be excluded from study participation.
- Able to be randomized prior to or up to 48 hours after surgery.

Exclusion criteria –

- Known history of seizure activity
- Pregnant or breastfeeding
- Renal dysfunction (CrCl<30ml/min)
- Beck's Depression Inventory (BDI) ≥14.(Subjects will have the BDI administered at baseline visit, prior to randomization. Those who score ≥14, will be excluded from the study and referred to clinical psychology. Subjects who select "2" or "3" on question 9, will be referred to clinical psychology without regard to the overall total score.)
- Allergy to levetiracetam

Research Plan:

After obtaining informed consent, subjects will be randomized into one of the following arms to receive study drug as follows:

1) Levetiracetam (Keppra at a daily dose of 1000mg (administered as one 500 mg tablet)PO twice daily for one (1) week.
2) Levetiracetam (Keppra) at a daily dose of 1000mg (administered as one 500 mg tablet)PO twice daily for six (6) weeks.

A simple randomization scheme will be used and will be generated by our statistician. All patients will be weaned off of the AED over 2 days by decreasing the dose to 500mg po every day for 2 days and then stop. The taper is to commence at day 5 for the one week group and at 2 days prior to the stop date for the 6 week group. The taper will be included on their prescription instructions and in the patient's discharge instructions to ensure proper taper of the drug. As is protocol, patients are given verbal instructions of all of their discharge medications prior to discharge along with a "teach back" method to confirm they understand how to take and stop their medications when they go home. Patients will begin study medication 48 hours post-op, regardless if they are discharged or remain hospitalized. At discharge, they will continue the medication regimen for the amount of time they were randomized.

Participants will maintain a diary that will collect seizure occurrences and daily medication intake. The RedCap database will be used to collect patient data. Participants will also complete the Beck Depression Inventory (BDI) and Neurotoxicity Scale[7] to assess mood changes and level of cognitive functioning at baseline (preoperatively or 24-48hrs postoperatively) and at 6 weeks postoperatively. Patients with a BDI score suggestive of mild mood disturbance or depression (BDI score ≥ 14) will be further evaluated by the Principal Investigator. This evaluation may include discontinuing leveteracitam, the initiation of antidepressant medications, or referral to clinical psychology. Patients will be followed until study completion and study activities will be conducted per the following Table of Events.

Activity	**Baseline** (24-48 hours post-op)	**Study Completion**** 6 weeks postop (*+/- 4days*)
Inclusion/exclusion criteria	**X**	
Informed consent	**X**	
Dispense prescription	**X**	
Dispense diary	**X**	
Collect or record diary data		**X**
Beck Depression Inventory (BDI)	**X**	**X**
Neurotoxicity Scale	**X**	**X**

**May be completed during a routine office visit or by telephone

Data will be collected by the clinical trial coordinator and kept in an encrypted and password protected database in the coordinator's locked office. Only the investigators and study coordinator will have access to the data with identifiers. At the conclusion of the study, the data will be deidentifed and the key will be kept in a secure location in the coordinator's locked office. The key will be kept until the study is completed and the manuscript is accepted for publication.

Subjects will be assigned a unique ID number and the following data points will be captured in the RedCap database:

- Unique study ID number
- Complete past medical and surgical history
- Family history of seizures
- Tumor pathology results
- Tumor imaging findings
- Concomitant Medications
- Neurotoxicity scale scores
- BDI scores
- Seizure Diary responses

- Records of side effects or symptoms experienced

Adverse events will be collected by the study coordinator at the six week evaluation or sooner if the patient contacts their physician/study team about new symptoms/problems. These events will be documented in the RedCap database. To ensure subject safety, each adverse event will be reviewed by an independent medical monitor (Dr. Stephan Eisenschenk) to determine if it is treatment-related. After each treatment-related adverse event that is "Serious and probable" or "Serious and definite" is identified, the study statistician will use a dynamic sequential testing method to determine if the proportion of enrolled patients who have experienced these types of adverse events up to that time has statistically exceeded a maximum acceptable proportion of 10%[8]. This method employs a concave alpha-spending function that allows a greater chance of detecting an unacceptably high adverse event rate earlier in the study while maintaining a nominal one-sided Type I error rate of 10% over the entire sequence of tests. Using a similar sequential testing approach, the odds ratio for experiencing a treatment-related adverse event between the two arms of the study will be tested for difference from 1 .after each adverse event, at a nominal two-sided sequence-wide Type I error rate of 20%. If either the maximum acceptable adverse event rate is exceeded, or odds ratio foradverse events between the 2 study arms is found to differ from one, study enrollment will be stopped for further evaluation of patient safety.

At the completion of the study, the scores on the neurotoxicity scale will be compared between the two groups. The analysis will be performed in an intent-to-treat manner. The groups will be compared using the Mann-Whitney test for the neurotoxicity scores and Fisher's exact test for the seizure rates. Using the neurotoxicity scale, we will need 38 patients in each group to show a difference of 5.4 points in the scale with a power of 80%. The maximum score on the scale is 81[7].

Possible discomforts or risks: Study participants may suffer from seizures related to their brain tumor or demonstrate side effects from using levetiracetam which may include:

- Sleepiness
- Weakness
- Infection
- Dizziness

Other possible risks of levetiracetam may include:

- Mood and behavior changes such as aggression, agitation, anger, anxiety, apathy, mood swings, depression, hostility, irritability and psychotic symptoms
- Hallucinations delusions and unusual behavior.
- Extreme sleepiness, tiredness, and weakness
- Problems with muscle coordination (problems walking and moving)
- Skin rash or serious dermatological reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis.
- Suicidal behavior or ideation

These side effects are uncommon. If participants demonstrate side effects from levetiracetam that are not tolerable, they may be weaned off and kept off AEDs if they are seizure free. The seizure rate and medication related side effect is not expected to be any higher than other patients treated for brain tumors.

Possible Benefits: The patients who are taken off of levetiracetam after one week will have lower medication costs and may experience less medication side effects.

Conflicts of Interest: None

References

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