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Levetiracetam (Keppra) efficacy and safety in the prevention of early-onset seizures following traumatic brain injuries in pediatric patients

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Abstract

Introduction: Approximately half a million emergency department visits for traumatic brain injury (TBI) by children and adolescents occur each year. One of the complications of TBI is early-onset seizure. Current guidelines recommend the use of phenytoin for prevention of seizures following a TBI; however, several drug interactions and adverse reactions are associated with its use. Despite studies demonstrating efficacy of levetiracetam in adult patients, the efficacy and safety of levetiracetam in children with TBI is unknown. The purpose of this study was to determine the efficacy and safety of levetiracetam for the prevention of early-onset seizures in pediatric patients following TBI.

Methods: A retrospective evaluation was conducted, which included children, ages 0 to 17 years, admitted secondary to a nonpenetrating TBI and who received levetiracetam for seizure prophylaxis for up to 7 days. The primary outcome was the number of children who had a seizure within the first 7 days following a TBI, and secondary outcomes included the number of adverse drug reactions.

Results: A total of 89 pediatrics patients with nonpenetrating TBI were identified and included in the study. Forty-seven patients received a mean dose of 10 mg/kg (SD ± 4.22) of levetiracetam twice a day, and 42 patients received 500 mg 2 times per day (based on adult dosing). Seizure activity was observed in only two patients (2.2%) within the first 7 days following TBI. A total of 13 patients (14.6%) experienced anemia, agitation, and elevation of liver enzymes during levetiracetam therapy.

Discussion: The study suggests that levetiracetam appears to be an effective and safe agent for early-onset seizure prophylaxis in pediatric patients with TBI as indicated by the low number of patients with seizures. The reported adverse reactions may have resulted from the trauma rather than the use of levetiracetam.

Keywords: levetiracetam, seizures, traumatic brain injury, pediatrics

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The Centers for Disease Control and Prevention reports nearly half a million emergency department visits occur annually for traumatic brain injuries (TBI) in children up to 14 years of age, with the highest rates occurring in

children less than 4 years.[1] TBI causes a variety of physical, cognitive, emotional, and behavioral complications particularly in pediatric patients. Post-traumatic seizure is one complication that may result from a direct insult of the trauma or pathophysiologic results of the trauma (eg, increased free radicals, increased glutamate in the central nervous system).[2] Pediatric patients are at higher risk for post-traumatic seizure than adults secondary to differences in cerebral circulation of blood and the increased susceptibility of apoptosis of cells in the neurons.[3]

Current guidelines recommend consideration of phenytoin for use after severe TBI for seizure prophylaxis.[4] However, phenytoin has multiple drug-drug interactions and potential harmful adverse reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, anticonvulsant hypersensitivity syndrome, and purple glove syndrome. Phenytoin also requires therapeutic drug monitoring as the pharmacokinetics can be altered in the critically ill patient. Additionally, in pediatric patients, administration of fosphenytoin is preferred due to decreased adverse reactions over phenytoin during intravenous administration of the medication. Recent drug shortages of fosphenytoin limited the availability of fosphenytoin, necessitating the use of levetiracetam for the prophylaxis of seizures after TBI.

Levetiracetam was approved by the Food and Drug Administration in 1999 as adjunctive therapy for partial onset seizures (greater than 4 years of age), primary generalized tonic-clonic seizures (greater than 6 years of age), and myoclonic seizures (greater than 12 years of age). The exact mechanism of action of levetiracetam has not been clearly elucidated, but it is thought to regulate neuronal activity by decreasing excitability of neurons, thereby preventing seizure activity due to modulation of GABA and glycine.[5]

Studies in the adult population have demonstrated levetiracetam has the potential to serve as an alternative to phenytoin for post-traumatic seizure prophylaxis in adult patients.[6-9] However, the efficacy and safety of levetiracetam in children with TBI is unknown. The objective of this study is to determine the efficacy and safety of levetiracetam for the prevention of early seizures in pediatric patients with TBI.

Methods

Study Design and Patient Population

Children admitted to a local hospital with a Level 2 Trauma Center (at time of study, currently a Level 1 Provisional Trauma Center) for pediatric patients between August 1, 2008, and March 31, 2013, due to a nonpenetrating TBI were retrospectively evaluated. Medical electronic records systems were queried to identify all subjects who received levetiracetam for TBI during the specified time frame. Patients, ages 0 to 17 years, who received levetiracetam up to 7 days for short-term seizure prophylaxis were included. Patients were excluded if they were on antiepileptic medications prior to injury, pregnant, or incurred a devastating head injury with expected or confirmed brain death within 48 hours. The study was approved by the Institutional Review Board of the hospital and a local university.

Data obtained included patient demographics (eg, gender, age, race/ethnicity, weight), initial Glasgow Coma Scale (GCS), mechanism of injury, diagnosis, history of cranial surgery upon admission, dose of levetiracetam, duration of therapy, concomitant receipt of antiepileptic medications, adverse events, and seizure activities while on levetiracetam within 7 days of admission.

The primary outcome of the study was the number of children with a seizure within the first 7 days following TBI as measured by clinical observation and documentation of seizure-like activity. As no control group was established, the rate of seizures in the study population was compared to the reported rate of seizures during treatment with phenytoin available in the literature of 3.6% to 7%.[10-11] Secondary outcomes included report of probable adverse reactions of levetiracetam (eg, anemia, increased liver enzymes, and differences in behavior).

Results

A total of 105 pediatrics patients with TBI were identified, and 89 were included in this study. Sixteen patients were excluded due to an existing seizure disorder or death within 48 hours of trauma. The average age was 9 years (± 6 years), and the majority of the patients were adolescents, ages 12–17 years (48%). Only 14 (16%) infants were included this study. Most of the patients were male (70%). The primary cause of TBI was related to motor vehicle accidents, including recreational vehicles (eg, all-terrain vehicles). Other demographic data of included subjects are presented in Table 1.

Thirty-four (38%) patients were diagnosed with subdural hemorrhage, and 15 (17%) patients had subarachnoid hemorrhage. Eighteen (20%) patients were found to have skull fracture, and the remaining 22 (25%) were diagnosed with left frontal hemorrhage, intracranial hemorrhage, intraventricular hemorrhage, or diffuse axonal injury. The initial GCS upon arrival to the emergency department was 11 (± 4.7).

TABLE 1: Baseline demographics

Parameter	Study Population
Age	
Mean (SD)	9 (6.2) years
Infant (< 1 year)	14 (15.7%)
Children (1–11 years)	32 (36%)
Adolescents (12–17 years)	43 (48.3%)
Weight, mean (SD)	40.4 (27.8) kg
GCS	
Mean GCS Score (SD)	11 (4.7)
Number of subjects based on their GCS score (n = 89)	
No GCS score	2
Severe injury (≤ 8)	27 (31%)
Moderate injury (9 to 12)	12 (13.8%)
Minor injury (13 to 15)	48 (55.2%)
Gender	
Male	63 (70.9%)
Female	26 (29.2%)
Ethnicity (%)	
White	56 (63%)
Black	18 (20%)
Hispanic	10 (11%)
Asian	0 (0%)
Other	5 (6%)
Mechanism of injury	
Motor vehicle accident (including recreation)	37 (42%)
Fall	21 (24%)
Child abuse	15 (17%)
Other	16 (18%)
Number of subjects with concomitant antiepileptic therapy (n = 9)	
Phenytoin or fosphenytoin	6
Phenobarbital	4

Upon admission, a total of 30 (34%) patients required cranial surgeries. Of the 89 subjects, approximately one half received weight-based dosing with a mean dose of 10 (± 4.9) mg/kg of levetiracetam twice a day, with an average weight and age range of 20 kg and 0–16 years, respectively. The other half received standard adult dosing of 500 mg 2 times per day, with an age range of 9–17. The average weight of the patients who received the adult dose was 64 kg. The average length of the therapy was 9 days.

Seizure activity was observed in 2 (2.2%) of patients within the first 7 days following TBI. One of them had subdural hematoma and subarachnoid hemorrhage, and the other patient was diagnosed with epidural hematoma and subdural hematoma. Neither of them had a severe head injury based on their initial GCS scores (12 and 14), and only one of them had cranial surgery. Both children who had seizure activity received 10 mg/kg per dose of levetiracetam.

TABLE 2: Adverse events

Possible adverse event	Number of patients (n = 13)
Anemia	9
Agitation	2
Elevated liver enzymes	2

A total of 13 patients (14.6%) had documentation of anemia, agitation, and elevation of liver enzymes during levetiracetam therapy (Table 2).

Discussion

The findings support the use of levetiracetam as early-onset seizure prophylaxis status post-TBI given the low rate of seizures in this evaluation. Although 13 patients had a possible adverse reaction associated with levetiracetam, there were high possibilities that the majority of the reactions (ie, anemia and elevation of liver enzymes) were secondary to the traumatic event rather than the medication. Due to the retrospective nature of the design, it is hard to distinguish exact causes of the reactions.

To date, 2 other studies have evaluated the use of levetiracetam after TBI in pediatric patients.[12-13] One study, however, focused on the efficacy and safety of levetiracetam as prophylaxis in patients at high risk for developing a seizure disorder following TBI. Patients were considered to be high risk if they experienced intracranial hemorrhage, penetrating wound injury, depressed skull fracture with subdural tear, or experienced an early post-traumatic seizure. The pilot study evaluated 20 children, ages 6–17 years, and prospectively followed the patients for 2 years. In total, one patient treated with levetiracetam developed epilepsy. The study population was similar to our population in that the most common reason for the TBI was motor vehicle–related, they were predominately male, and initial GCS scores were 12.3 (± 3.5). However, doses of levetiracetam were much higher at 55 mg/kg/day divided twice daily. The study reported 20% of the children enrolled had experienced an early post-traumatic seizure, which made them eligible for inclusion in the study and initiated levetiracetam at that time. In our evaluation, children were started on levetiracetam prior to the onset of seizure to prevent early-onset seizures. The most commonly reported adverse reactions in the treatment group were headaches (55%), drowsiness or somnolence (45%), and transient psychosis in one patient, which resolved while still on levetiracetam. The lack of anemia and elevation of liver function tests in the

prospective study further strengthens our hypothesis that these were related to the trauma rather than the medication. The retrospective nature of our study and concomitant medications (eg, analgesics, sedatives) made it difficult to assess headaches and drowsiness in our study population.

The second study, published as an abstract, did not show efficacy of levetiracetam for prevention of seizure after a TBI. The prospective observational study included 35 children, of which 20% experienced a seizure within 7 days of TBI. The individuals in the study, however, had a lower GCS (median 8) compared to our study population, indicating less severe TBI in our population. A limitation of the study by Chung and O'Brien[13] includes a lack of details regarding dosing information and time to initiation of levetiracetam. The authors also report a much higher incidence of seizure following TBI of 20% to 40%, which may have resulted from the severity of injury in the patients included in the study. As noted in Table 1, more than half of the subjects in our evaluation had a minor injury based on GCS.

The more critical question that may arise at this time is whether early-onset seizure prophylaxis is necessary for all patients with TBI. Two studies have reported an incidence of early post-traumatic seizure between 5% and 12%.[12,14] However, both studies are limited by small sample size. Given that protocols between trauma centers and hospitals may vary in the use of antiepileptic agents in these patients, a true incidence of early-onset seizure is unknown.

In determining which patients should receive early-onset seizure prophylaxis following TBI, clinicians must consider the benefit-risk ratio of antiepileptic medications and the development of a seizure. Pediatric patients have lower seizure thresholds than adults, which may warrant a more aggressive prophylaxis approach. Additionally, pediatric patients may have a higher amount of subclinical seizures or seizures that are more difficult to detect than adult counterparts, particularly in the very young[15] and those who may be medically sedated or paralyzed, leading to further cognitive impairment. Specific risk factors for the development of a seizure following TBI are listed in Table 3. One study found independent risk factors for early post-traumatic seizure in children less than 2 years of age (odds ratio [OR] 3.0 [95% CI 1.0, 8.6]), nonaccidental trauma (OR 3.0 [95% CI 1.0, 11.3]), or GCS less than or equal to 8 (OR 8.7 [95% CI 1.1, 67.6]).[14] Given the aforementioned risks, these patients may likely benefit from prophylaxis.

The selection of a specific antiepileptic medication is dependent on various factors. Both phenytoin and levetiracetam appear to be efficacious. Phenytoin may be limited by a higher incidence of severe adverse reactions, requirement of therapeutic drug monitoring, and alterations of pharmacokinetics in critical patients. Although levetiracetam has not been used as extensively as phenytoin, the adverse reactions in pediatric patients are milder with the exception of the behavioral abnormalities. Therapeutic drug monitoring does not appear to be necessary in this setting as one study has demonstrated no changes in pharmacokinetic parameters from day 3 to day 30 following a TBI.[15] Another advantage to levetiracetam is the quicker time to establish steady-state concentrations than phenytoin. Given that many of the early onset seizures occur within 24 to 48 hours after the trauma, achieving steady state sooner may result in increased protection against seizures.[16]

TABLE 3: Risk factors for development of post-traumatic seizure in pediatric patients

Risk factors
Society of Critical Care Medicine[4]
Location of the lesion (not specified)
Cerebral contusions
Retained bone and metal fragments
Depressed skull fracture
Focal neurologic deficits
Loss of consciousness
Glasgow Coma Scale score less than 10
Severity of injury
Length of post-traumatic amnesia
Subdural or epidural hematoma
Penetrating injury
Leisemer et al[14]
Age less than 2 years
Severe traumatic brain injury
Nonaccidental trauma
Prehospital hypoxia
Impact seizure
Subdural hemorrhage

The current study is not without limitations. As the study was retrospective in nature, it is unknown what the true incidence of seizure activity was. Seizure activity may not have been witnessed by anyone, or it may not have been documented in the medical record. Additionally, evaluation of adverse reactions is limited to medical documentation and may not be all-inclusive. Also, our study was a single center study, which has limitations regarding external validity and scientific rigor. Another limitation is the lack of a control group in our study. In the time period that was used for inclusion, only levetiracetam was used for seizure prophylaxis following TBI. It was decided not to use a case-controlled design as many confounding factors existed. However, the low rate of seizure in the study

population suggests the agent was beneficial in preventing the early onset of seizures.

Conclusion

The results of our retrospective study suggests levetiracetam may be an effective and safe agent for early-onset seizure prophylaxis in children with TBI as indicated by the low number of patients with seizures. However, future studies to determine children at highest risk for development of early-onset seizure are necessary.

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