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Early Post-traumatic Seizure Occurrence in Pediatric Patients Receiving Levetiracetam Prophylaxis With Severe Traumatic Brain Injury

Meghan J. Kolf, PharmD; Christopher C. McPherson, PharmD; Kara S. Kniska, PharmD; Caitlyn M. Luecke, PharmD; Michael A. Lahart, PharmD; and Jose A. Pineda, MD

OBJECTIVE Although levetiracetam is used for the prevention of early Post-traumatic seizures (EPTS) after traumatic brain injury (TBI), limited data exist describing the incidence of seizures in pediatric patients receiving levetiracetam prophylaxis. The objective of this research is to evaluate the prevalence of EPTS in children given prophylactic levetiracetam after severe TBI.

METHODS This study was conducted at a Level 1 pediatric trauma center and included pediatric patients with severe TBI who received levetiracetam for EPTS prophylaxis. Demographics and clinical information were retrospectively collected and evaluated. The primary outcome was prevalence of clinical or electrographic seizures within 7 days of initial injury as noted in the EMR.

RESULTS In 4 of 44 patients (9%), seizures developed despite levetiracetam prophylaxis. Concurrent use of other medications with antiepileptic properties was common (91%). There were no differences in demographic or baseline clinical characteristics between the group of patients experiencing seizures and those who did not. However, craniotomy was significantly more common in the seizure group (75% vs. 18%, p = 0.03).

CONCLUSIONS Children receiving prophylaxis with levetiracetam after severe TBI had a lower incidence of seizures (9%) than had previously been reported in the literature (18%). Given the limited literature available supporting the use of levetiracetam for the prevention of EPTS in children experiencing severe TBI, further study is needed to support routine use.

ABBREVIATIONS EEG, electroencephalogram; EMR, electronic medical record; EPTS, early post-traumatic seizures; FDA, US Food and Drug Administration; GCS, Glasgow Coma Scale; ICP, intracranial pressure; IV, intravenous; PICU, pediatric intensive care unit; TBI, traumatic brain injury

KEYWORDS anticonvulsants; head injury; levetiracetam; pediatrics; prophylaxis; seizures; traumatic brain injury

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Introduction

The incidence of traumatic brain injury (TBI) has steadily increased in the United States over the last decade and remains a major cause of morbidity and mortality among pediatric patients. Just under half a million children younger than 15 years of age are evaluated annually in the emergency department for TBI.[1] There are a number of mechanisms of injury associated with TBI that can be particularly problematic in the developing pediatric patient. Early post-traumatic seizures (EPTS) occurring after TBI have the ability to perpetuate ongoing neurological damage and affect the long-term quality of life and developmental outcomes of pediatric patients.[2,3]

Due to the potential lasting sequelae from EPTS, some institutions have begun using antiepileptic therapy prophylactically for prevention of EPTS. However, due to lack of data and ambiguous recommendations in the guidelines, practice is highly variable.[4] Historically, prophylactic phenytoin has been used for the prevention of EPTS after TBI. A large randomized controlled trial in adult patients with TBI support its use.[5] The second edition of the pediatric TBI guidelines published in 2012 included a level III recommendation that phenytoin specifically be considered for the prevention of EPTS.[4] In a retrospective study, children with severe TBI who received prophylactic phenytoin had a 15% prevalence of EPTS compared with 53% in children who received no antiepileptic medications.[6] Additionally, a more recent study found antiepileptic drugs, including phenytoin, fosphenytoin, and phenobarbital, protective against EPTS.[7] However, because of many adverse effects, a narrow therapeutic index, and highly variable

pharmacokinetic properties in critically ill children, many institutions avoid phenytoin use.[8]

In 2006, levetiracetam was FDA approved as an IV antiepileptic agent with less documented adverse effects when compared with older antiepileptic agents like phenytoin.[9] Additionally, no significant drug interactions have been reported, and it does not cause enzymatic induction or inhibition. Consequently, in both pediatric and adult populations, there has been an increase in the use of levetiracetam in place of phenytoin for the prevention of EPTS.[10–12] Despite this general shift in practice, there are sparse data examining the efficacy of levetiracetam for this indication in the pediatric population. The updated third edition of the guidelines for the management of severe TBI published in 2019 continue to recommend EPTS prophylaxis but no longer specifically recommend phenytoin. There was also a statement added to the guidelines stating that levetiracetam could not be recommended over phenytoin based on either efficacy or toxicity.[7,13–15]

To date, there has been 1 prospective study examining the incidence of EPTS in patients who received prophylaxis with levetiracetam after TBI. A group of 34 pediatric patients with moderate to severe TBI were evaluated; 6 patients experienced EPTS despite levetiracetam prophylaxis, resulting in a seizure incidence of 17.6%.[14] Based on historically reported lower seizure incidence in patients receiving phenytoin prophylaxis (2%–15%) compared with their described incidence with levetiracetam prophylaxis, the authors concluded that levetiracetam may not be an equally efficacious agent when compared with phenytoin for the prevention of EPTS after TBI.

Despite this concern, levetiracetam continues to be used in clinical practice. Based on the gap between current literature and clinical practice, there is the need for further evaluation of levetiracetam for the prevention of EPTS. To address limitations of previous studies, mainly the inclusion of multiple injury severities, we conducted a retrospective study in which the primary objective was to report the incidence of EPTS in pediatric patients given prophylactic levetiracetam after severe TBI.

Materials and Methods

A retrospective study was conducted at St. Louis Children's Hospital in St. Louis, MO, a pediatric Level 1 trauma center. Patients admitted to the PICU with severe TBI from October 2006 to August 2017 and receiving levetiracetam for EPTS prophylaxis were identified from an internal Virtual PICU Systems database with subsequent chart reviews conducted for inclusion and exclusion criteria. EPTS was defined as the occurrence of clinical or electrographic (subclinical) seizures in the first 7 days after TBI. Severe TBI was defined as an initial recorded or admission Glasgow Coma Scale (GCS) score of ≤ 8.[4,13] Initial GCS scores were defined as the first GCS score recorded in the field or upon admission to the emergency department, and admission GCS score was defined as the first GCS score recorded upon admission to the PICU. Patients were excluded if they experienced a seizure prior to the initiation of levetiracetam, if they had a history of seizures or a seizure disorder, or if they were declared brain dead or expired < 48 hours after admission.

Management of TBI was at the discretion of the medical team and was guided by the institutional TBI protocol and published pediatric TBI guidelines. Of note, continuous EEG monitoring is not a standard of care and was initiated if there was concern for subclinical seizures, if patients were receiving neuromuscular blockade, or if pentobarbital was used for intracranial pressure (ICP) management.

Demographic information including age, gender, and mechanism of injury were recorded. Clinical or electrographic seizures in the first 7 days after injury were recorded based on documentation in the EMR by an intensivist or consulting neurologist. Dosing of levetiracetam was recorded in addition to the use of other medications with antiepileptic properties (including pentobarbital, diazepam, midazolam, and lorazepam) during the 7 days after initial injury. Presence or absence of fever, defined as temperature greater than or equal to 38°C, and nadir sodium level during PICU stay was collected because of associated seizure risk. Data related to severity of injury, including the use of additional monitoring methods, hyperosmolar agents, and the need for surgical interventions, were also collected.

Statistical analysis was performed using SPSS 19 (SPSS, Inc, Chicago, IL). Descriptive statistics were used to describe the overall seizure incidence rate. Patients who experienced EPTS and those who did not were compared using Fisher exact test for categorical variables and Mann-Whitney *U* test for continuous variables. A p value of < 0.05 was used to define statistical significance.

Results

A total of 275 patients admitted to the PICU with TBI were identified. One-hundred fifty-two patients were excluded for an initial or admission GCS of > 8. Fifty-six patients were excluded for prior seizure activity. Twenty-three patients were excluded because they did not receive any seizure prophylaxis. Baseline demographic data of the remaining 44 patients included in the study can be found in the Table.

Seizures were noted in 4 of the 44 children who received prophylaxis with levetiracetam. One patient presented clinically and was confirmed with EEG; subclinical seizures in 3 patients were detected by continuous EEG, which was used because of the presence of a pentobarbital coma, a coma from injury, and use of

Table. Patient Demographic Data and Comparison of Clinical Information for Patients With Seizures and Without Seizures

Patient Characteristic	All Patients (N = 44)	Patients Without Seizures (n = 40)	Patients With Seizures (n = 4)	p value
Age, yr, median (IQR)	7.5 (2–12)	7.5 (2–12)	7.5 (4–12)	0.89
Sex, male, n (%)	25 (57)	24 (60)	1 (25)	0.30
GCS score				
Earliest score, median (IQR)	5 (3–7)	4.5 (3–6.8)	7.5 (4–8)	0.22
Admit score, median (IQR)	5.5 (3–6)	6 (3–6)	3 (3–7.5)	0.37
Mechanism of injury—abusive head trauma, n (%)	7 (16)	5 (13)	0 (0)	0.71
Test/procedure				
ICP monitor, n (%)	25 (57)	22 (55)	3 (75)	0.62
Continuous EEG monitor, n (%)	27 (61)	23 (58)	4 (100)	0.15
Febrile on PICU admission, n (%)	35 (80)	31 (78)	4 (100)	0.57
Nadir sodium level, median (IQR)	139 (137–142)	139 (137–141)	141 (135–144)	0.49
Management				
Craniotomy, n (%)	10 (23)	7 (18)	3 (75)	0.03
Hypertonic saline, n (%)	30 (68)	27 (68)	3 (75)	1
Mannitol, n (%)	25 (57)	22 (55)	3 (75)	0.62
Levetiracetam, mg/kg/dose	10 (5–20)*	10 (5–30)†	10 (10–12)†	0.60
Other medications with antiepileptic properties, n (%)	40 (91)	36 (90)	4 (100)	0.18
Barbiturates	3 (7)	2 (5)	1 (25)	
Benzodiazepines	27 (61)	26 (65)	1 (25)	
Barbiturate and benzodiazepine	10 (23)	8 (20)	2 (50)	
Survived, n (%)	39 (89)	36/40 (90)	3/4 (75)	0.39

* Median (IQR).
† Median (range).

a paralytic for ventilator synchrony. This resulted in an overall seizure incidence rate of 9%. Overall, 91% of the patients included had received other medications with antiepileptic properties ranging from low dose benzodiazepines for sedation to barbiturate-induced comas for refractory elevated ICP.

When comparing patients who experienced seizures to those who did not, there were no statistically significant differences found in baseline demographics (Table). There were also no significant differences in the initial or admission GCS scores or dose of levetiracetam between the groups. Continuous EEG monitoring was common and not significantly different between groups. There were significantly more craniotomies in children experiencing seizures. Notably, there was not a significant difference found between the 2 groups when the mechanism of injury was abusive head trauma. The use of other antiepileptic medications was not found to be significantly different between patients experiencing seizures and seizure-free patients.

Discussion

In our cohort, patients receiving levetiracetam after severe TBI experienced seizures at a rate of 9% despite prophylaxis. These patients were more likely to have had craniotomies and many were placed on continuous EEG monitoring, potentially alluding to clinical concern for a significant degree of brain damage. There were no significant differences in baseline demographics for patients experiencing seizures compared with patients who did not seize.

To our knowledge, this is the largest study focusing on the prevalence of seizures after severe TBI in pediatric patients receiving levetiracetam prophylaxis. A seizure incidence of 9% is lower than historically reported incidence rates for patients receiving no prophylaxis (20%–53%) and is within range for patients receiving phenytoin prophylaxis (2%–15%).[6,14] In contrast to a previous study, the seizure incidence in this cohort did not suggest that prophylaxis with levetiracetam was less efficacious than phenytoin in the prevention of

EPTS in pediatric patients with severe TBI.[14] Collectively, these data support the conclusion that levetiracetam use was associated with a lower seizure incidence when compared with patients receiving no prophylaxis historically. However, it is important to note the overall advancements in the medical management of pediatric patients with TBI when interpreting historically reported seizure incidence rates.

Given the differing seizure incidence rates reported between our cohort and the previous study, it is important to evaluate differences in the included patient populations.[14] There were no notable differences in demographic information, including median age, between the 2 populations that would serve as a possible explanation for the difference in seizure rates. The inclusion of patients with moderate TBI in the study by Chung and O'Brien[14] resulted in a higher median GCS score, which would suggest a lower potential for seizures in their cohort. The use of other medications with antiepileptic activity, including benzodiazepines and barbiturates, represents a confounding factor that must be evaluated. The use of benzodiazepines for sedation and barbiturates for refractory elevated ICP are common in the management of TBI and are both outlined in the pediatric TBI guidelines.[4,13] Although 91% of patients receiving medications with antiseizure activity is a confounding factor in evaluating the use of levetiracetam for the prevention of EPTS, the use of these medications is a standard of care and would likely be a similar finding in future or previous studies conducted in this patient population. The use of antiepileptic medications for all patients was not included in previous studies for comparison.

In both our cohort and the cohort studied by Chung and O'Brien,[14] there was a similar percentage of patients sustaining a TBI as a result of an abusive head trauma or non-accidental trauma.[14] However, in the previous study, all of the patients experiencing breakthrough EPTS also experienced TBIs as a result of abusive head traumas. This was not the case in our patient population, in which no patient experienced EPTS from a TBI with abusive head trauma as the etiology.

Differences seen in TBI patient populations regarding the incidence of EPTS may be attributed to the fact that TBI is a dynamic disease state with multiple factors affecting subsequent sequelae, including EPTS. There are several risk factors for EPTS after TBI described in the literature, including abusive head trauma as a mechanism of injury.[7] Abusive head trauma is associated with potential repetitive injury over time and there is often uncertainty surrounding the timeline of initial injury, adding difficulty to the interpretation of true EPTS in the first 7 days after injury. Therefore, variation in the timeline and frequency of abusive head trauma may be an explanation for the observed difference in seizure incidence rate in these 2 groups of pediatric patients. This observed difference highlights the importance of looking at a significant number of patients in the pediatric TBI population when assessing the efficacy of seizure prophylaxis after TBI.

There were a number of limitations in this study. Primarily, this was a small, single-center study and may not represent the pediatric TBI population as a whole. Although still small, our sample focused on severe TBI only, including more patients with severe injury than the previous study. All patients were not placed on continuous EEG monitoring because this is not a standard of care in our PICU. Although the effect of subclinical seizures on outcome after severe TBI are still being characterized, due to a lack of EEG monitoring on all patients, there is the possibility that subclinical seizures were not captured or documented in the medical record, and the actual incidence of clinically relevant seizures may be higher than reported. Ninety-one percent of patients in this study received other medications with antiseizure properties making the effect of levetiracetam specifically less clear. Finally, this study was both retrospective and observational, prohibiting prospective attention to protocol adherence. Based on the small sample size of this study and the noted limitations, further studies are needed to assess the use of levetiracetam in the prevention of EPTS after severe TBI.

Conclusions

Breakthrough EPTS occurred in 9% of pediatric patients receiving levetiracetam prophylaxis after severe TBI in our cohort. This is a lower seizure incidence than had previously been reported with this therapy. Further studies are needed to examine the use and efficacy of levetiracetam for the prevention of EPTS in children after severe TBI.

ARTICLE INFORMATION

Affiliations Department of Pharmacy (MJK, CCM, KSK, CML, MAL), St. Louis Children's Hospital, St. Louis, MO, Department of Pediatrics (CCM, JAP), Washington University School of Medicine, St. Louis, MO

Correspondence Meghan J. Kolf, PharmD; mkolf@iuhealth.org

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Ethical Approval and Informed Consent Given the nature of this study, the institution review board/ethics committee did not require HIPAA Waiver of Authorization, Waiver of Assent, and Waiver of Parental Permission under Exempted criterion.

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REFERENCES

1. Centers for Disease Control and Prevention. Web-based injury statistics query and reporting system. https://www.cdc.gov/traumaticbraininjury/data/index.html. Accessed October 1, 2017.
2. DelSignore LA, Tasker RC. Treatment options for severe traumatic brain injuries in children: current therapies, challenges, and future prospects. *Expert Rev Neurother.* 2017;17(12):1145–1155.
3. Catroppa C, Anderson VA, Morse SA, et al. Outcome and predictors of functional recovery 5 years following pediatric traumatic brain injury (TBI). *J Pediatr Psychol.* 2008;33(7):707–718.
4. Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents–second edition. *Pediatr Crit Care Med.* 2012;13(suppl 1):S1–82.
5. Temkin NR, Dikmen SS, Wilensky AJ, et al. A randomized, double blind study of phenytoin for the prevention of post-traumatic seizures. *N Engl J Med.* 1990;323(8):497–502.
6. Lewis RJ, Yee L, Inkelis SH, et al. Clinical predictors of post-traumatic seizures in children with head trauma. *Ann Emerg Med.* 1993;22(7):1114–1118.
7. Liesemer K, Bratton SL, Zebrack CM, et al. Early post-traumatic seizures in moderate to severe pediatric traumatic brain injury: rates, risk factors, and clinical features. *J Neurotrauma.* 2011;28(5):755–762.
8. Wolf GK, McClain CD, Zurakowski D, et al. Total phenytoin concentrations do not accurately predict free phenytoin concentrations in critically ill children. *Pediatr Crit Care Med.* 2006;7(5):434–439.
9. Radic JA, Chou SH, Du R, Lee JW. Levetiracetam versus phenytoin: a comparison of efficacy of seizure prophylaxis and adverse event risk following acute or subacute subdural hematoma diagnosis. *Neurocrit Care.* 2014;21(2):228–237.
10. Kruer RM, Harris LH, Goodwin H, et al. Changing trends in the use of seizure prophylaxis after traumatic brain injury: a shift from phenytoin to levetiracetam. *J Crit Care.* 2013;28(5):883.e9–13.
11. Zafar SN, Khan AA, Ghauri AA, et al. Phenytoin versus levetiracetam for seizure prophylaxis after brain injury—a meta-analysis. *BMC Neurol.* 2012;12:30.
12. Szaflarski JP, Sangha KS, Lindsell CJ, et al. Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis. *Neurocrit Care.* 2010;12(2):165–172.
13. Kochanek PM, Tasker RC, Bell MJ, et al. Management of pediatric severe traumatic brain injury: 2019 consensus and guidelines-based algorithm for first and second tier therapies. *Pediatr Crit Care Med.* 2019;20(3):269–279.
14. Chung MG, O'Brien NF. Prevalence of early Post-traumatic seizures in children with moderate to severe traumatic brain injury despite levetiracetam prophylaxis. *Pediatr Crit Care Med.* 2016;17(2):150–156.
15. Pearl PL, McCarter R, McGavin CL, et al. Results of phase II levetiracetam trial following acute head injury in children at risk for Post-traumatic epilepsy. *Epilepsia.* 2013;54(9):e135–e137.