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Early Post-Traumatic Seizures in Moderate to Severe Pediatric Traumatic Brain Injury: Rates, Risk Factors, and Clinical Features

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Abstract

We performed a retrospective, observational study at a level I pediatric trauma center of children with moderate-to-severe traumatic brain injury (TBI) from January 2002 to September 2006 to identify clinical and radiographic risk factors for early post-traumatic seizures (EPTS). Two hundred and ninety-nine children ages 0–15 years were evaluated, with 24 excluded because they died before the initial head computed tomography (CT) was obtained ($n=20$), or because their medical records were missing ($n=4$). Records were reviewed for accident characteristics, pre-hospital hypoxia or hypotension, initial non-contrast head CT characteristics, seizure occurrence, antiepileptic drug (AED) administration, and outcome. All care was at the discretion of the treating physicians, including the use of AEDs and continuous electroencephalogram (EEG) monitoring in patients receiving neuromuscular blocking agents. The primary outcome was seizure activity during the first 7 days as determined by clinician observation or EEG analysis. Of the 275 patients included in the study, 34 had identified EPTS (12%). Risk factors identified on bivariable analysis included pre-hospital hypoxia, young age, non-accidental trauma (NAT), severe TBI, impact seizure, and subdural hemorrhage, while receiving an AED was protective. Independent risk factors identified by multivariable analysis were age <2 years (OR 3.0 [95% CI 1.0,8.6]), Glasgow Coma Scale (GCS) score ≤8 (OR 8.7 [95% CI 1.1,67.6]), and NAT as a mechanism of injury (OR 3.4 [95% CI 1.0,11.3]). AED treatment was protective against EPTS (OR 0.2 [95% CI 0.07,0.5]). Twenty-three (68%) patients developed EPTS within the first 12 h post-injury. This early peak in EPTS activity and demonstrated protective effect of AED administration in this cohort suggests that to evaluate the maximal potential benefit among patients at increased risk for EPTS, future research should be randomized and prospective, and should intervene during pre-trauma center care with initiation of continuous EEG monitoring as soon as possible.

Key words: CT scanning; epilepsy; pediatric brain injury; secondary insult

Introduction

Traumatic brain injury (TBI) is a major health problem for American children that causes over 2000 deaths per year, and has devastating consequences for many survivors (Faul et al., 2010). Management of TBI is aimed at minimizing secondary injury due to hypoxia, hypercarbia, systemic hypotension, intracranial hypertension, and increased metabolic demand (Bruce, 1990).

Seizures are one cause of increased metabolic demand after TBI. Post-traumatic seizures (PTS) are commonly classified by time of occurrence. Impact seizures occur within the first moments after injury. Early post-traumatic seizures (EPTS) are seizures occurring within the first week after injury but not immediately after impact, while late PTS are those occurring after the first week. EPTS are associated with worse outcome in infants and children suffering from both accidental and inflicted injury (Chiaretti et al., 2000; Keenan et al., 2007; Ong et al., 1996), and seizure prevention may be a potential intervention to improve outcomes after TBI.

Current guidelines for the management of severe TBI in children, defined as a Glasgow Coma Score (GCS) ≤8,

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recommend consideration of prophylactic anti-epileptic drugs (AED) in patients at high risk for EPTS (Adelson et al., 2003). Although AED prophylaxis is commonly used in clinical practice, studies investigating its efficacy fail to show consistent benefit, defined as EPTS prevention (Lewis et al., 1993; Young et al., 2004). Consensus management guidelines for severe TBI in adults also recommend consideration of prophylactic anti-epileptic therapy to prevent EPTS, yet both call for more research on AED selection, optimal timing, and effect on outcome (Bratton et al., 2007; Chang and Lowenstein, 2003).

Accurate identification of children at risk for EPTS can be difficult after moderate or severe TBI (Hahn et al., 1988; Lewis et al., 1993; Ratan et al., 1999). Younger age (Ong et al., 1996; Ratan et al., 1999), and more severe injury (Hahn et al., 1988; Marshall et al., 1992; Ong et al., 1996; Ratan et al., 1999), are the most consistently reported risk factors and are highlighted in the current guidelines for the management of severe TBI in children (Adelson et al., 2003). Identification of additional risk factors for EPTS may further clarify which patients are likely to benefit from targeted therapy with AED prophylaxis, and limit administration of AEDs to children at very low risk.

This study aims to identify additional risk factors for EPTS in children, focusing on factors that can be identified early after injury. We hypothesize that pre-hospital instability and intracranial pathology on the initial non-contrast head computed tomography (CT) scan will be associated with increased risk.

Methods

Patient selection

This is a retrospective, observational cohort study of 299 infants and children admitted to Primary Children's Medical Center (PCMC) from January 2002 to September 2006 with moderate to severe TBI. PCMC is a free-standing, level I trauma center that serves 6 states in the Western region of the United States, and had $\sim$1200 annual pediatric intensive care unit (PICU) admissions during the study period. Inclusion criteria were age <15 years and either moderate or severe TBI. Moderate TBI was defined as a post-resuscitation GCS score of 9–12, and severe TBI as a post-resuscitation GCS score of 3–8. The post-resuscitation GCS score was assigned by the trauma service in the PCMC emergency department (ED). Exclusion criteria were death before the initial non-contrast head CT was obtained or if the medical record could not be located. This cohort was first identified for a study investigating early resuscitation of children with moderate-to-severe TBI (Zebrack et al., 2009). This study was approved by the University of Utah Institutional Review Board and was granted a waiver of informed consent.

Study design

Variables selected for evaluation of a potential association with EPTS included age, severity of brain injury, and mechanism of injury. These were evaluated because prior studies have found them to be risk factors. In addition, pre-hospital instability and head imaging characteristics were included, as they are factors that are easily identified at hospital admission and are also reported to predict outcome after TBI (Chiaretti et al., 2002; Englander et al., 2003; King et al., 2005).

Data on patient past medical history, seizure activity, radiographic characteristics of the initial non-contrast head CT, EEG monitoring when used with administration of neuromuscular blocking agents (NMBA), and AEDs were collected to complement the initial cohort investigation. Data were obtained by chart review of both the electronic and paper medical records, as well as query of the PCMC Pharmacy database. There were no standard protocols in place for the use of AED prophylaxis or EEG monitoring of heavily sedated or chemically paralyzed patients with TBI; however, during the study period patients with intracranial hypertension (ICH) were managed using a protocol that mirrored the Brain Trauma Foundation's guidelines (Adelson et al., 2003).

Injury characteristics

Potential risk factors for EPTS based on characteristics of the injury such as pre-hospital instability (e.g., hypoxia or hypotension), severity of injury, and mechanism of injury were obtained. Mechanism of injury was divided into mechanized and non-mechanized, in which mechanized injuries were defined as those involving motor vehicle accidents, snowmobile and all-terrain vehicle (ATV) crashes, and pedestrian versus motor vehicles, and non-mechanized injuries were defined as those secondary to falls, bike accidents, sports injuries, and ski or snowboard injuries. Non-accidental trauma (NAT) was included as a separate mechanism of injury; the determination of NAT was made by the hospital's child abuse team. Hypoxia was defined as oxygen saturation <90%, and hypotension as systolic blood pressure less than the fifth percentile for the age-appropriate norm.

Non-contrast head CT characteristics

The first available non-contrast head CT for each patient was reviewed to identify specific injuries and assign a Marshall CT score (Marshall et al., 1992). Specific injuries evaluated included parenchymal contusions, intracranial hemorrhage, and depressed skull fractures. Parenchymal contusions were characterized by location as frontal, biparietal, or temporal, and by frequency as either single or multiple. Intracranial hemorrhage included epidural hematomas (EDH), subdural hematomas (SDH), subarachnoid hemorrhages (SAH), and intraventricular hemorrhages (IVH). All studies were read by a pediatric radiologist.

Seizure characteristics

We reviewed the emergency medical services (EMS) transport records and PCMC medical records during the first 7 days after admission or through hospital discharge, whichever came first, for information regarding seizures. Seizure activity was confirmed either by clinician documentation of rhythmic extremity or facial movement, autonomic instability, or by EEG analysis, when performed. Seizures were characterized by type as focal, focal then generalized, and generalized tonic-clonic. Impact seizures were defined as seizures occurring within the first 5 min after injury. Seizure occurrence after initial injury was grouped into 12-h intervals for the first 24 h, 24-h intervals for the next 48 h, and then as those occurring more than 72 h after injury. Seizures were defined as prolonged if they lasted 15 or more minutes, recurrent if there were two or more seizures in a 24-h period, and difficult to control if two or more AEDs were administered.

AED and NMBA use

The EMS and Life Flight transport records, PCMC ED trauma records, and medication administration records (MAR), were used to determine whether an AED was administered after injury but before an EPTS. The drug name, dosage, and frequency of administration were recorded. The decision to treat with an AED was at the discretion of the treating physicians. Patient records were also examined for use of NMBAs. NMBA use was defined by administration of at least two or more doses in a 24-h period.

Outcome measures

The primary outcome was the incidence of EPTS. Secondary outcomes included clinical characteristics associated with EPTS identified during the analysis. EPTS was evaluated for an association with odds of mortality or poor neurologic outcome at hospital discharge. Functional neurologic outcome was assessed at hospital discharge using the Glasgow Outcome Score (GOS), which ranges from 5 (good recovery) to 1 (death). We ranked the outcome as "good" if the GOS was 4 (mild disability) or 5 (good recovery), and "poor" if the GOS was 1 (dead), 2 (severely disabled), or 3 (moderately disabled).

Statistical analysis

Data were analyzed using SPSS 18.0.0 for Windows (SPSS Inc., Chicago, IL). Summary statistics were presented as medians (with 25th and 75th quartiles) or percentages. Bivariable analyses were performed using the χ^2 and the Mann-Whitney U tests. Statistical significance was defined as $p < 0.05$.

A multivariable analysis was performed to evaluate independent potential associations between EPTS and prehospital instability, injury mechanism, initial non-contrast head CT characteristics and demographic features. Variables considered in the multivariable model included those that were significantly associated with EPTS in the bivariable analysis. Variables were entered in a stepwise forward logistic regression model, and the variables were initially entered if $p < 0.1$, and were excluded if $p > 0.05$. Adjusted odds ratios (ORs) with 95% confidence intervals were calculated.

Results

Of the 299 patients with moderate-to-severe TBI initially identified for inclusion in this study, 20 were excluded because they died before the initial head CT was done and 4 were excluded because their medical records could not be obtained (Fig. 1). The excluded children tended to have more severe TBI (92% with GCS ≤ 8 versus 72% in the study population), and higher Injury Severity Score (ISS; median ISS 40 versus 25). Of the 275 patients included in this study, 34 patients (12%) had one or more seizures identified within the first 7 days after injury (Table 1). There was no significant difference in gender, ethnicity, or past medical history in patients with or without EPTS. Patients with EPTS were younger, with 53% of patients < 2 years of age, compared to only 12% of patients with no seizures or impact seizures only. Functional outcome, discharge to inpatient rehabilitation and long-term care facilities, and mortality did not differ between children with EPTS and those without seizures.

Injury characteristics

The risk of EPTS was similar for both mechanized and non-mechanized mechanism of injury; however, children with EPTS were more likely to have injuries secondary to NAT (Table 2). NAT was identified in 38% of children with EPTS but only 8% of those without seizures. Patients with EPTS sustained more severe TBI as evidenced by 97% of patients with EPTS having a post-resuscitation GCS score ≤ 8 compared to 78% of patients with no seizure or impact seizure

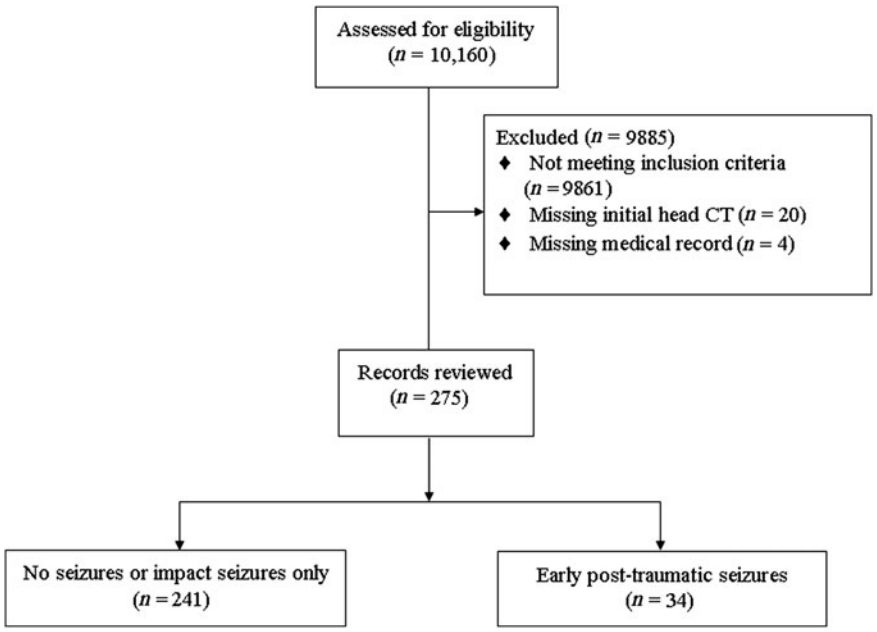

FIG. 1. Flow chart of study entry (CT, computed tomography).

Table 1. Demographic Characteristics of Children with Moderate to Severe Traumatic Brain Injury (TBI) Categorized by Absence or Presence of Early Post-Traumatic Seizures (EPTS)

	No seizures or impact seizure only N = *241* n *(%)*	*EPTS* N = *34* n *(%)*	p *Value*
Gender			0.32
Male	149 (62)	24 (71)	
Age (years)			<0.01
Median (25th IQR, 75th IQR)	7.4 (3.2, 11.9)	1.4 (0.4, 5.7)	<0.01
<2	30 (12)	18 (53)	
2–4	59 (24)	7 (21)	
5–10	65 (27)	4 (12)	
>10	87 (36)	5 (15)	
Ethnicity			0.47
White	175 (73)	23 (68)	
Other[a]	37 (15)	8 (23)	
Unknown	29 (12)	3 (9)	
Past medical history[b]			
Seizures	4 (2)	1 (3)	0.57
Stroke	0 (0)	0 (0)	0.35
Prior TBI	7 (3)	0 (0)	0.38
Developmental delay	15 (6)	1 (3)	0.20
Glasgow Outcome Scale score			0.16
Good outcome (4–5)	183 (76)	22 (65)	
Poor outcome (1–3)	58 (24)	12 (35)	
Discharge to inpatient rehabilitation or long-term care facility	42 (17)	6 (18)	0.44
Mortality	42 (17)	3 (9)	0.20

[a]The majority of the population in Utah is white.
[b]Six (2%) patients without seizures died before history could be obtained.
IQR, interquartile range.

only, and had a longer PICU length of stay. There was no difference in the Injury Severity Score (ISS), rates of other organ system involvement, blood gas pH measurements, or rate of ICP monitoring. Although pre-hospital hypoxia occurred more frequently in the EPTS group, there was no difference in pre-hospital hypotension. Of the 34 children with identified EPTS, 6 children (18%) also had an impact seizure prior to onset of EPTS, compared to only 12 (5%) in the no seizure group.

Head CT characteristics

Marshall CT score categories were not associated with risk of EPTS (Table 3). Of the children with identified EPTS, 56% had Marshall CT scores of I or II, meaning either no visible pathology or only diffuse injury without signs of increased intracranial pressure. This proportion was similar to that observed in the group with no seizures. The frequency of frontal, biparietal, single or multiple parenchymal contusions did not differ between groups. Interestingly, presence of a parenchymal contusion in the temporal lobe, while an infrequent occurrence, was observed in 12% of patients in the no seizure group compared with 0% in the EPTS group. Similarly, the presence of any contusion, regardless of location, was significantly more frequent in the no seizure group (44% vs. 24% in the EPTS group). The occurrence of EDH, SAH, or IVH did not differ between groups, and there was no difference in presence of a depressed skull fractures. In contrast, SDH was significantly more common among children with identified EPTS than those with no seizures (65% vs. 39%).

Seizure characteristics of children with EPTS

The majority of EPTS occurred within the first 12 h after injury with only 18% occurring more than 72 h after injury (Table 4). Although patients with identified EPTS were observed for significantly longer in the hospital, the majority of both groups of patients were observed for the full 7 days: 74% of patients in the EPTS group and 52% in the no seizure group. Focal seizure activity was the most common seizure type followed by generalized tonic-clonic activity. Patients with EPTS were more likely to have received an EEG during their PICU stay, 29% compared to 10% in the no seizure group. Only half of the EEGs performed were continuous in either group with more in the EPTS group, 18% versus 5% in the no seizure group. Most patients who developed EPTS had prolonged or recurrent seizures, but only 18% required ≥ 2 AEDs for control.

AED and NMBA use

Although only half of the 275 children in this cohort were started on an AED, the majority were in the no seizure group, with only 24% of EPTS patients started on an AED prior to an EPTS (Table 5). The majority of patients started on AED prophylaxis were treated with fosphenytoin, 97% in the no seizure group and 50% in the EPTS group. Once started on an AED, most patients received a full 7-day course, although it is interesting to note that 38% of the patients in the no seizure group were taken off of prophylaxis during the first 7 days.

The majority of NMBA use occurred on the first day, although less than half of each study group received two or more doses (Table 5). From a peak of 44% in the no seizure group and 38% in the EPTS group, use steadily declined with no significant difference in NMBA use between study groups on any of the observed days.

Independent risk factors

Bivariable analysis of potential factors identified age < 2 years, severe TBI, NAT versus other mechanism of injury, pre-hospital hypoxia, impact seizure, subdural hemorrhage, and AED prophylaxis ($p < 0.05$). On multivariable analysis, age < 2 years, severe TBI, and NAT remained independently associated with EPTS, while treatment with an AED was protective (Table 6). Risk of EPTS increased threefold (OR 3.0 [95% CI 1.0,8.6]) with age < 2 years, more than eightfold with severe TBI (OR 8.7 [95% CI 1.1,67.6]), and more than threefold when NAT was the mechanism of injury (OR 3.4 [95% CI 1.0,11.3]). Administration of an AED significantly reduced the risk of EPTS (OR 0.2 [95% CI 0.07,0.5]) in this cohort.

Discussion

EPTS have been associated with worse outcomes in pediatric patients with TBI (Chiaretti et al., 2000; Keenan et al.,

Table 2. Injury Characteristics of Children with Moderate to Severe Traumatic Brain Injury (TBI) Categorized by Absence or Presence of Early Post-Traumatic Seizures (EPTS)

	No seizures or impact seizure only N = *241* n *(%)*	*EPTS* N = *34* *n (%)*	p *Value*
Mechanism of injury			<0.01
Non-accidental trauma	19 (8)	13 (38)	
Mechanized	105 (44)	12 (35)	
Non-mechanized	117 (49)	9 (26)	
Glasgow Coma Scale (GCS) score			<0.01
Moderate TBI (GCS[a] 9–12)	53 (22)	1 (3)	
Severe TBI (GCS[a] 3–8)	188 (78)	33 (97)	
Markers of injury severity			
Hypoxia[b]	89 (37)	20 (59)	0.02
Hypotension[b]	86 (36)	10 (29)	0.47
Impact seizure	12 (5)	6 (18)	0.01
pH[c] (median [25th IQR, 75th IQR)	7.34 (7.26, 7.38)[d]	7.32 (7.22, 7.37)	0.40
ISS (median [25th IQR, 75th IQR)	25.0 (16.0, 33.0)	25.0 (16.8, 26.3)	0.48
ICP[e] monitor placed	91 (38)	13 (38)	0.96
PICU LOS (days) median (25th IQR, 75th IQR)	2.0 (1.0, 6.0)	6.0 (2.0, 9.0)	<0.01

[a]Post-resuscitation GCS score.
[b]31% were not monitored for hypotension and 34% were not monitored for hypoxia during part of the pre-hospital care.
[c]Initial pH obtained in our emergency department.
[d]pH not obtained in 9 patients.
[e]Refers to both extraventricular drains and intraparenchymal fiberoptic monitors.
IQR, Interquartile range; ICP, intracranial pressure; ISS, Injury Severity Score; LOS, length of stay; NMBA, neuromuscular blocking agent; PICU, pediatric intensive care unit.

2007; Ong et al., 1996). Our aim was to identify risk factors for EPTS apparent in the first hours after injury, allowing for improved and earlier identification of patients at risk for this complication. In our population of children with moderate to severe TBI, the incidence of EPTS was 12%. Younger age (< 2 years), severe TBI, and NAT were independently associated with EPTS, and treatment with an AED was protective. The majority of EPTS were focal and occurred within the first 12 h after injury. Most seizures were prolonged or recurrent, but typically responded to treatment with a single AED.

Table 3. Radiographic Characteristics of Children Categorized by Absence or Presence of Early Post-Traumatic Seizures (EPTS)

	No seizures or impact seizure only N = *241* n *(%)*	*EPTS* N = *34* n *(%)*	p *Value*
Marshall CT score			0.77
I: No visible intracranial pathology	59 (24)	7 (21)	
II: Cisterns present with 0–5 mm of shift	86 (36)	12 (35)	
III: Cisterns compressed or absent with 0–5 mm of shift	54 (22)	7 (21)	
IV: Midline shift > 5 mm but no lesion > 25 cm^3	6 (2)	0 (0)	
V: Any lesion surgically evacuated	30 (12)	7 (21)	
VI: Any high or mixed density mass lesion > 25 cm^3 not surgically evacuated	6 (2)	1 (3)	
Parenchymal contusion[a]			
Temporal lobe	28 (12)	0 (0)	0.04
Any contusion	106 (44)	8 (24)	0.04
Intracranial hemorrhage			
Epidural hematoma	30 (12)	2 (6)	0.26
Subdural hematoma	93 (39)	22 (65)	<0.01
Subarachnoid hemorrhage	55 (23)	9 (26)	0.64
Intraventricular hemorrhage	28 (12)	2 (6)	0.32
Depressed skull fracture	52 (22)	7 (21)	0.90

[a]Each head CT was evaluated for the presence of frontal, temporal, and parietal specifically by location as well as the presence of multiple parenchyma contusions.
CT, computed tomography.

Table 4. Seizure Characteristics of Early Post-Traumatic Seizures (EPTS)

	EPTS N = *34* n *(%)*
Seizure type	
Focal	25 (74)
Focal then generalized	3 (9)
GTC	5 (15)
Not recorded	1 (3)
Seizure occurrence	
30 min–11 h	23 (68)
12–23 h	1 (3)
24–47 h	3 (9)
48–72 h	1 (3)
>72 hours	6 (18)
Difficult to control (required two or more AEDs for control)	6 (18)
Prolonged (≥15 min length) orRecurrent (≥2 seizures/24 h)	24 (71)

GTC, generalized tonic-clonic; EEG, electroencephalogram; AED, antiepileptic drug.

Our cohort corroborates the previously established EPTS risk factors of age < 2 years (Ong et al., 1996; Ratan et al., 1999), and severe TBI (Hahn et al., 1988; Marshall et al., 1992; Ong et al., 1996; Ratan et al., 1999), as well the less consistently reported risk factor of NAT (Barlow et al., 2000; Keenan et al., 2003), and SDH (Hahn et al., 1988; Ong et al., 1996). It also identified two other risk factors for EPTS: pre-hospital hypoxia and impact seizures. The pathophysiological link between isolated hypoxia without hypotension and EPTS is unclear. Impact seizure has not been well studied as a risk factor for EPTS in children, but if confirmed by additional studies may aid in patient selection for prophylactic treatment. The association between impact seizures and EPTS is hard to compare with previous studies of adults and children because they were not separately evaluated (Chiaretti et al., 2000; Lowenstein, 2009; Ratan et al., 1999).

Table 5. Antiepileptic Drug (AED) and Neuromuscular Blocking Agent (NMBA) Use in Children with Moderate to Severe Traumatic Brain Injury (TBI) Categorized by Absence or Presence of Early Post-Traumatic Seizures (EPTS)

	No seizures or impact seizure only N = *241* n *(%)*	*EPTS* N = *34* n *(%)*	p *Value*
Received an AED before seizure			<0.01
Yes	125 (52)	8 (24)	
No	116 (48)	26 (76)	
AED used			<0.01
Fosphenytoin or phenytoin	123 (51)	3 (9)	
Phenobarbital	2 (1)	4 (12)	
Other[a]	0 (0)	1 (3)	
Completed AED course[b]	78 (32)	8 (24)	<0.01
Continuous EEG monitoring	12 (5)	6 (18)	<0.01
NMBA use			
Day 1	106 (44)	13 (38)	0.53
Day 2	79 (33)	13 (38)	0.53
Day 3	58 (24)	9 (26)	0.76
Day 4	39 (16)	10 (29)	0.06
Day 5	34 (14)	7 (21)	0.32

[a]Patient treated with both fosphenytoin and phenobarbital.
[b]Received 7 days of treatment with AED.
EEG, electroencephalogram.

Table 6. Multivariable Logistic Regression Model: Risk of Early Post-Traumatic Seizures (EPTS) in Children

	Odds ratio	*95% Confidence interval*
Mechanism of injury		
NAT	3.4	1.0–11.3
Other mechanism	1	Reference group
Severity of TBI		
Severe TBI	8.7	1.1–67.6
Moderate TBI	1	Reference group
Patient age		
0–2 years	3.0	1.0–8.6
≥2 years	1	Reference group
Preventive administration of AED	0.2	0.07–0.5

NAT, non-accidental trauma; TBI, traumatic brain injury; AED, antiepileptic drug.

Similarly to previous studies of EPTS that reported that most EPTS occurred in the first 24 h after injury (Chiaretti et al., 2000; Hahn et al., 1988; Lewis et al., 1993; Ong et al., 1996; Ratan et al., 1999), we found that the majority were identified in the first 12 h with a second, much smaller peak after 72 h. This early peak may limit optimal prophylaxis of EPTS with AEDs if prophylaxis is not initiated early enough after injury, or if a medication that takes longer to achieve steady state is selected. The majority of EPTS were focal, followed by generalized tonic-clonic seizures. Previous studies investigating EPTS have also reported that focal seizures are more common (Chiaretti et al., 2000; Ong et al., 1996), although one study found a higher incidence of generalized seizures (Hahn et al., 1988).

We examined AED use at our institution and found that treatment with an AED was protective against EPTS. The success of AED prophylaxis has not been consistently demonstrated, with previous studies showing both positive (Lewis et al., 1993) and negative effects (Young et al., 2004). In this study we could not determine if therapeutic drug levels were achieved. The vast majority of patients were treated with fosphenytoin or phenytoin, and there was inconsistent monitoring of drug levels, thus limiting conclusions. For these reasons, any conclusions about AED prophylaxis in this study are limited, but it does support further prospective, randomized research in this area.

There were additional limitations to this study inherent to its design as a retrospective, observational cohort study. While management of ICH followed a protocol that mirrored the Brain Trauma Foundation's treatment guidelines (Adelson

et al., 2003), management was otherwise determined by the treating physicians, including treatment with a NMBA, use of EEG monitoring, and placement of an ICP monitor. Seizure activity was attributed to a patient based on several factors, including observation by bystanders, EMS personnel, and medical providers at our institution, as well as by select use of EEG tracing. Given our long transport times (148 min median time in the entire cohort with no significant difference between groups), some clinical seizures may not have been recognized. Less than 15% of the study cohort was monitored for seizures using EEG tracings, but 44% of the no seizure group and 38% of the EPTS group received two or more doses of an NMBA on the first day after injury. In adult studies of continuous EEG, more than half of the patients identified as having EPTS demonstrated non-convulsive seizures that would not have been identified without EEG monitoring (Vespa et al., 1999). Future studies should consider utilizing continuous EEG monitoring on all paralyzed patients to avoid under-detection of EPTS. While NMBA use steadily decreased in both groups during the 7 days of observation, with no significant difference in use by study group, the presence of unmonitored patients increases the possibility of missed seizures.

Data on pre-hospital instability were collected from EMS run sheets, which were not always completely filled out, leading to periods when the patients were not fully monitored. This absence of vital sign data may have led to an under-estimation of the incidence of hypoxia and/or hypotension. Misclassification of these exposures might alter any associations reported for EPTS. In addition, we had limited statistical power to determine if multiple variables were independently associated with EPTS due to the relatively low incidence. Furthermore, children with mild TBI were not included, limiting comparisons with less severe head injury.

Finally, inherent to all retrospective studies, data were collected from multiple sources, including EMS run sheets, the PCMC pharmacy database, and the electronic and paper medical records. It is assumed that all data were entered accurately, but this is difficult to guarantee when information is not collected prospectively.

Author Disclosure Statement

No competing financial interests exist.

The views expressed in this article are those of the authors and do not reflect the offical policy or position of the Department of the Army, Department of Defense, or the U.S. Government.

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