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Abusive Head Trauma and Mortality – An Analysis from an International Comparative Effectiveness Study of Children with Severe Traumatic Brain Injury

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Abstract

Objectives—Small series have suggested that outcomes after abusive head trauma (AHT) are less favorable than after other injury mechanisms. We sought to determine the impact of AHT on mortality and identify factors that differentiate children with AHT from those with TBI from other mechanisms.

Design—First 200 subjects from the Approaches and Decisions in Acute Pediatric TBI (ADAPT) Trial – a comparative effectiveness study using an observational, cohort study design.

Setting—Pediatric intensive care units in tertiary children's hospitals in USA and abroad.

Participants—Consecutive children (age <18 y) with severe TBI (GCS ≤ 8; intracranial pressure (ICP) monitoring).

Interventions—None

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Measurements and Main Results—Demographics, injury-related scores, prehospital and resuscitation events were analyzed. Children were dichotomized based on likelihood of AHT. A total of 190 children were included (n = 35 with AHT). AHT subjects were younger (1.87 y ± 0.32 vs. 9.23 y ± 0.39, p < 0.001) and a greater proportion were female (54.3% vs. 34.8%, p = 0.032). AHT were more likely to (i) be transported from home (60.0% vs. 33.5%, p < 0.001), (ii) have apnea (34.3% vs. 12.3%, p = 0.002) and (iii) seizures (28.6% vs. 7.7%, p < 0.001) during pre-hospital care. AHT had a higher incidence of seizures during resuscitation (31.4 vs. 9.7%, p = 0.002). After adjusting for covariates, there was no difference in mortality (AHT, 25.7% vs. non-AHT, 18.7%, HR 1.758, p = 0.60). A similar proportion died due to refractory intracranial hypertension in each group (AHT, 66.7% vs. non-AHT, 69.0%).

Conclusion—In this large, multicenter series, children with AHT had differences in prehospital and in-hospital secondary injuries which could have therapeutic implications. Unlike other TBI populations in children, female predominance was seen in AHT in our cohort. Similar mortality rates and refractory ICP deaths suggest that children with severe AHT may benefit from therapies including invasive monitoring and adherence to evidenced-based guidelines.

Keywords

pediatric traumatic brain injury; abusive head injury; comparative effectiveness research; pediatric neurocritical care; secondary injuries

Introduction

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality in children (1) and abusive head trauma (AHT) remains a mechanism of injury unique to children. Previous work has shown have shown worse outcomes in AHT children compared to other mechanisms of TBI (2, 3). It is unclear if this relationship is due to the age of these children (as AHT children are more likely to be ≤ 2 y) or if pathological mechanisms unique to AHT are responsible for the relationship (2, 4–6). With the large gap in our knowledge about the pathophysiology of AHT and the lack of evidence regarding treatments specific to children with such an injury, the current evidenced-based guidelines have been unable to make substantive recommendations regarding this unique population (7). This has negatively impacted the identification and development of therapeutic targets to improve outcome in this patient population and argues for our need to better understand children with AHT.

At present, AHT has recognizable differences in several clinical and pathophysiologic features. AHT can often include acceleration/deceleration forces, multiple injuries and a delay in presentation to medical care. Diffuse axonal injury, subdural hemorrhage (from shearing of bridging vessels) with some degree of hypoxia are commonly reported (8–10). A recent review found that AHT children - of all severities of injury - have 20% mortality and almost 50% permanent disability rates (11). Keenan and colleagues found children with AHT had worse outcomes at 1 year post-injury (12) and that children with AHT (i) were younger, (ii) had extracranial fractures, (iii) retinal hemorrhages, (iv) older injuries, (v) subdural hemorrhage, (vi) seizures and (vii) cerebral edema (13). In another study, only 15% of AHT patients had a good outcome at a mean of 8 years after injury whereas 40% had severe neurological impairment (14). Among children with AHT, risk factors for mortality

include low initial GCS score, retinal hemorrhage, intraparenchymal hemorrhage, and cerebral edema (15). Lastly, AHT is associated with financial, emotional and societal costs. Xiang and colleagues found that hospital charges for AHT patients to average approximately $30,000 (4). The average hospital costs for AHT in the U.S. was $69.6 million (16). This estimate did not consider ongoing medical needs which Lind and colleagues found that 83% of AHT children required at median follow-up of 8 y after injury (14). Survivors are estimated to exceed 24 disability adjusted life years (DALY), defined as years lost due to disability/death, while even mild AHT exceeds the burden estimated for children with severe burn injuries (17). Finally, AHT children incur medical costs years after their initial injury, an average of $47,952 in the 4 years following the event (18).

Due to the alarming consequences of AHT and severe limitations of our understanding of this population, we chose to analyze the first 200 children in the ADAPT Trial to better understand this population as rapidly as possible. In this analysis, we determined factors associated with AHT and the impact of AHT on mortality.

Methods

The ADAPT trial is a comparative effectiveness study of children with severe TBI funded via a cooperative agreement with NINDS (U01 NS081041). The overall goal of the study is to compare the effectiveness of strategies related to intracranial hypertension, secondary injuries and metabolic support in 1000 children from centers (n = 51) in the US, UK, Spain, the Netherlands, India, South Africa, Australia and New Zealand. All centers received Institutional Review Board approval (or equivalent) for performing the study and the University of Pittsburgh received IRB approval to coordinate the study. The study design of the ADAPT trial is strictly observational – sites care for children based on their local standards of care without interventions. Due to this study design and the need to minimize selection bias, all sites were granted permission by their IRB/Ethics Board to collect data regarding the acute hospitalization on all children who met inclusion criteria/exclusion criteria (inclusion: age < 18 y, diagnosis of severe TBI [Glasgow Coma Scale (GCS) score ≤ 8], placement of intracranial pressure (ICP) monitor at study site; exclusion: pregnancy). Informed consent was obtained for follow-up activities including mortality assessments. Therefore, the subjects in this report represent *consecutive eligible subjects admitted to study sites*.

In this analysis, data from the first 200 subjects enrolled in the study (February 22, 2014 – December 22, 2014) were analyzed. The analysis was designed to determine factors associated with AHT and the role of AHT with mortality. This analysis was performed at this juncture because (i) the sample size of 200 is one of the larger populations of children with severe TBI in the literature to date and (ii) the desire to inform the pediatric neurotrauma community of compelling findings in a timely manner. Demographic characteristics, injury details, injury-related scores (Abbreviated Injury Scores [AIS], Injury Severity Scores [ISS], Pediatric Risk of Mortality [PRISM] III scores), prehospital events and resuscitation events were collected. Definitions of these variables are provided in the supplementary material. Mortality (defined as death within the study period – up to 1 year after ICP monitor placement) was collected as the outcome for this analysis. The cause of

death was stratified (multisystem trauma, refractory intracranial pressure, medical complications) and recorded from the medical record. Prehospital events were defined as events that occurred from the time the injury until presentation to the study hospital. Resuscitation events were defined as events that occurred from the time of admission to the study hospital until the ICP monitor was placed.

Data Stratification and Data Analysis

AHT was stratified based on the certainty of the clinicians at the clinical site regarding the diagnosis of AHT (Table 1). For this analysis, we combined “Probable AHT” and “Definite AHT” (defined as “AHT”) children and compared this group to those without suspicion of AHT (defined as “No AHT”). Children initially classified as “Possible AHT” were excluded from this analysis because the circumstances were too vague to categorize the subjects. The demographic and clinical characteristics are reported by subgroup as means ± SEM for continuous variables and percentages for discrete variables. T-tests were used to test the equality of the means across the group for continuous variable and chi-square tests were used to compare percentages for discrete variables. When test assumptions were not met, the non-parametric Wilcoxon test was used to compare between-group means and Fisher’s exact test was used to compare the distributions of percentages. The association of AHT with mortality was assessed using standard survival analyses techniques. A log-rank test was used to assess for differences between the two curves. To control for confounding effects, a multi-variable Cox proportional hazards model was used to assess the independent association of AHT on mortality. A bivariate proportional hazards model was also estimated for comparison.

Results

There were a total of 190 children included in this analysis (10 were excluded as “possible AHT”). Of the 190 children, 35 were classified as AHT. Demographics are presented in Table 2. Those with AHT were younger (1.87 y ± 0.32 vs. 9.23 y ± 0.39, $p < 0.001$) and a greater proportion were female (54.3% vs. 45.7%, $p = 0.032$). There were 26 children from international study sites (defined as sites outside of the United States) and none were diagnosed with AHT. There was no difference in AIS and ISS scores between groups except for thoracic scores were lower in AHT children (Table 3). There was also no difference in GCS score (5.03 ± 0.32 vs. 5.32 ± 0.15, $p = 0.354$).

In the prehospital phase of care, children with AHT were more likely to have been transported from home (60% vs. 33.5%, $p < 0.001$), more likely to have apnea (34.3% vs. 12.3%, $p = 0.002$) and seizures (28.6% vs. 7.7%, $p < 0.001$). There was no difference in rates of hypoxemia or hypotension between AHT and the non-AHT groups in the pre-hospital care (2.9% vs. 7.1%, $p = 0.61$; 8.6% vs. 15.5%. $p = 0.67$; respectively). During the resuscitation phase of care, seizures were also more common in children with AHT (31.4% vs. 9.7%, $p = 0.002$; Table 4). There again was no difference observed between rates of hypoxemia and hypotension in AHT compared to non-AHT groups (5.7% vs. 3.2%, $p = 0.62$; 34.3% vs. 29.0%, $p= 0.54$; respectively). Children with AHT received more

barbiturates (17.1% vs. 3.9%, p = 0.010) and had decreased hemoglobin levels (9.78 g/dl ± 0.37 vs. 11.3 g/dl ± 0.15, p ≤ 0.001).

There was no difference in mortality between AHT and the non-AHT groups (25.7% vs. 18.7% respectively; adjusted HR 1.758, p = 0.60 after adjustments, see Table 5). The majority of deaths in both groups were due to increased ICP (AHT, 66.7%; non-AHT, 67.9%). PRISM III scores were not different between AHT and non-AHT groups (19.2 ± 3.26 vs. 17.2 ± 1.38, p = 0.25).

Discussion

In severe pediatric TBI, the diagnosis of child abuse – with its pathophysiological sequelae - can have implications on many factors that may affect outcome. Over the last several years, a knowledge gap has been identified regarding children with AHT within the literature, especially in terms of management and therapeutic targets. Given the lack of guideline-based recommendations for therapy specifically for severe AHT, insight into epidemiology, management, and outcome in severe AHT - particularly when ICP monitoring and ICP-directed therapy is used - is desperately needed. AHT is more likely to include intracranial hemorrhage, damage in the craniocervical junction, respiratory compromise, shock and cerebral edema (19, 20). Predictors of poor outcome include depth of coma, cerebral edema, hypoxia-ischemia, PRISM scores, retinal/intraparenchymal hemorrhages (15, 21, 22). Indeed, AHT represents a distinct clinical and pathophysiologic entity of TBI.

Our study used the first 200 prospectively recruited children in the ADAPT trial, which focuses on severe TBI cases where ICP monitoring and ICP-directed management was used. While other series may have contained more AHT subjects, our report reflects consecutive patients cared for at more than 50 sites across the developed world – thereby reflecting a comprehensive examination of clinical care over approximately 1 year of patient screening. AHT victims have been consistently reported in the literature to be younger than children with accidental TBI (23–27), which our study confirmed. In contrast to most AHT cohorts, we found a female predominance in the population of AHT (3, 15, 16, 23, 24, 28–30). We found one other study that showed a female predominance in AHT (31). Our study differed from others in the literature in that included children all had ICP monitors placed – which may have altered the relationship between gender and AHT in some unexplained manner. One could speculate that gender may impact the injury response to explain the female predominance, but our study cannot support any conclusions for this hypothesis (32–34). There does not appear to be a cultural bias from international site enrollments, as we did not identify any children (male or female) from the international sites with AHT in this cohort.

We found that children with AHT were more likely to have seizures and apnea before arrival to the study hospital, and seizures were also more common during the resuscitation phase of care. These findings are consistent with a recent study by Greiner and colleagues that found over 25% of their population with AHT had non-convulsive seizures (35) as well as other reports (36, 37). A recent meta-analysis found that seizures and apnea were significantly associated with AHT, supporting our findings (27). Johnson and colleagues found that the majority of their AHT cohort had apnea prior to arrival at the hospital (38). Interestingly,

even though there was a high incidence of apnea in children with AHT in our study, there was no significant difference in hypoxemia between groups in both the pre-hospital and resuscitation phases. This may be in part due to the definition of “hypoxemia” used in the ADAPT trial, which is defined as a $SaO_2 < 90\%$ for 30 minutes.

Finally, we found that children with AHT were more frequently transported from home. This finding is consistent with the presumption that caregivers of children with AHT may be perpetrators of the injury, thus being more reticent to activate the emergency medical system (13). While our data cannot provide information as to the circumstances surrounding these decisions, it does suggest that prehospital care of children with AHT may differ substantially from other children with TBI. Specifically, transport to the hospital by private vehicle without trained personnel could lead to the under-diagnosis/treatment of secondary insults. Differences in prevalence of seizures and apnea could either be explained by a delay in presentation for the AHT group, or by the fact that these groups are affected by different mechanisms of injury.

Since seizures were more common, it is not surprising that barbiturates were administered more often to the AHT group. We also found that children with AHT had decreased hemoglobin levels compared to accidental TBI. This could be explained by the younger age of children with AHT and their proximity in age to their physiological hemoglobin nadir (6 - 8 weeks of age). Others have shown a decrease in hematocrit associated with AHT, and this finding was shown to be an important component to a decision rule in diagnosing AHT (31, 39, 40). There was no difference in neurological exam except for the lowest recorded GCS score, which was decreased in the AHT group. Consistent with our GCS finding, Hymel and colleagues and Goldstein and colleagues found a similar relationship between lowest GCS score and AHT (19, 41). Finally, another study reported that children with AHT were more likely to have a GCS score of 3 - 8 (OR 2.99) as compared to children with accidental TBI (42).

In contrast to previous reports, we did not find a difference in mortality between the AHT and non-AHT groups. Previous studies have generally been limited by sample size, retrospective design and lack of control of confounding factors. Xiang and colleagues found the case mortality rate was 53.9 per 1000 patients with AHT compared to 1.6 per 1000 patients with accidental TBI (4). There have been other reports of 3 – 6 fold increase in mortality rates in AHT when compared to accidental TBI (25, 26, 43). All of these studies have included all severities of injury and have not required an ICP monitor for inclusion. We believe that our data on children with severe AHT being monitored/treated for intracranial hypertension are of special importance because they represent children who were being treated in centers committed to care based on the published guidelines. We also found that a similar percentage of children died from refractory ICP in both groups. This is a novel and potentially important finding particularly given the well-known paucity of ICP monitoring in young children (some presumed to have AHT) reported by Bennett and colleagues (44). Our finding certainly suggests that victims of AHT have increased ICP and could likely benefit from ICP monitoring and ICP-directed therapy as others have suggested (45).

Our study has limitations, including a relatively small sample size of AHT children. Nevertheless, we feel that this cohort from multiple centers remains valuable, particularly due to the large number of covariates available for analysis and the consecutive nature of subject enrollments. We believe that it is important to disseminate the current findings to the pediatric neurotrauma community to manage this important public health problem as the parent study is completed. A second limitation of the study is the reliance on site personnel to identify cases of definite and probable AHT. As sites may have different systems of detecting such a disorder, our study is necessarily reliant on the clinical sites for this determination. Third, our study is necessarily reliant on information from medical records, including reports from parents, regarding important aspects under study. In particular, our finding that prehospital apnea was common in children with AHT must take into account that many of these children were transported to the hospital from home – and the ability of caregivers to report physiological findings is limited. Nevertheless, we were able to identify that prehospital apnea was commonly found in children with AHT. Lastly, there is an unavoidable selection bias for children who received ICP monitoring as part of their clinical care. While this limits our overall understanding of AHT children with the entire spectrum of TBI severity, we believe that this intentional selection of children infers that ICP monitoring in AHT children can lead to similar mortality rates compared to children with accidental injuries.

In conclusion, we found a predominance of younger and female children within our AHT cohort of consecutive children across dozens of clinical sites in the developed world. Seizures and apnea occurred early, demonstrating the need for careful monitoring of children suspected of AHT. While there was no difference in mortality between groups, a similar percentage of children in both groups died from increased ICP, further suggesting AHT children might benefit from ICP monitoring and ICP-directed therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

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Table 1

Definition of Abusive Head Trauma within the ADAPT Trial

Likelihood of Abusive Head Trauma (AHT)	Definition
None	No evidence within the medical records that AHT is being considered
Possible AHT	Clinical notes indicate that AHT is in the differential diagnosis of the treating team, but the diagnosis of AHT has not been made
Probable AHT	Clinical notes indicate that the treating team believes that the child suffered from AHT
Definite AHT	Confirmed diagnosis of intentional trauma and AHT is documented by a physician within the medical record

Table 2

Demographic and injury measures by abusive head trauma

Measure	Total (N=190)	Abuse		Analysis	
		Yes (N=35)	No (N=155)	Test statistic	p
Age	**7.87 ± 0.39**	**1.87 ± 0.32**	**9.23 ± 0.39**	**U(1) = 59.8**	**<.0001**
Sex				**χ^2(1) = 4.56**	**0.0326**
Female	73 (38.4)	19 (54.3)	54 (34.8)		
Male	117 (61.6)	16 (45.7)	101 (65.2)		
Race				χ^2(2) = 1.68	0.4320
White	126 (66.3)	20 (57.1)	106 (68.4)		
Black	40 (21.1)	9 (25.7)	31 (20.0)		
Other	24 (12.6)	6 (17.1)	18 (11.6)		
Weight (kg)	**32.7 ± 1.69**	**10.1 ± 0.89**	**37.8 ± 1.82**	**U(1) = 62.8**	**<.0001**
Primary language				TP(0) = 0.06	0.6776
English	168 (89.4)	33 (94.3)	135 (88.2)		
Spanish	14 (7.4)	1 (2.9)	13 (8.5)		
Sign	1 (0.5)	0 (0.0)	1 (0.7)		
Other	5 (2.7)	1 (2.9)	4 (2.6)		
Cause of injury				**χ^2(3) = 148**	**<.0001**
Motor vehicle	101 (53.2)	0 (0.0)	101 (65.2)		
Accidental fall	28 (14.7)	2 (5.7)	26 (16.8)		
Homicide/assault	36 (18.9)	32 (91.4)	4 (2.6)		
Other	25 (13.2)	1 (2.9)	24 (15.5)		
Type of injury				TP(0) < 0.01	0.1258
Closed	168 (88.4)	35 (100)	133 (85.8)		
Penetrating	14 (7.4)	0 (0.0)	14 (9.0)		
Blast	1 (0.5)	0 (0.0)	1 (0.6)		
Crush	7 (3.7)	0 (0.0)	7 (4.5)		
Mechanism of injury				**TP(0) < 0.01**	**0.0027**
Acceleration/Deceleration	26 (13.9)	11 (33.3)	15 (9.7)		
Direct impact/Fall	142 (75.9)	22 (66.7)	120 (77.9)		

Measure	Total (N=190)	Abuse		Analysis	
		Yes (N=35)	No (N=155)	Test statistic	p
Penetrating	12 (6.4)	0 (0.0)	12 (7.8)		
Other	7 (3.7)	0 (0.0)	7 (4.5)		
Likelihood under the influence				TP(0) = 0.07	0.1651
None	176 (96.7)	34 (97.1)	142 (96.6)		
Suspected	1 (0.5)	1 (2.9)	0 (0.0)		
Confirmed	5 (2.7)	0 (0.0)	5 (3.4)		
Transported to study hospital from				**TP(0) < 0.01**	**<.0001**
Scene of injury	107 (56.3)	6 (17.1)	101 (65.2)		
Home	73 (38.4)	21 (60.0)	52 (33.5)		
Other hospital	10 (5.3)	8 (22.9)	2 (1.3)		
Glasgow coma scale	5.27 ± 0.14	5.03 ± 0.32	5.32 ± 0.15	U(1) = 0.86	0.3536
International site	**26 (13.7)**	**0 (0.0)**	**26 (16.8)**	**TP(0) < 0.01**	**0.0052**

NOTE: TP indicates Fisher's exact test

Table 3

Severity scores and pre-hospital events by abusive head trauma

		Abuse		Analysis	
Measure	**Total (N=190)**	**Yes (N=35)**	**No (N=155)**	**Test statistic**	**p**
Abbreviated Injury Scale					
Head	4.26 ± 0.06	4.46 ± 0.12	4.21 ± 0.07	U(1) = 1.92	0.1660
Face	0.97 ± 0.08	0.66 ± 0.13	1.05 ± 0.09	U(1) = 2.82	0.0929
Neck	0.19 ± 0.05	0.09 ± 0.05	0.21 ± 0.06	U(1) = 0.26	0.6092
Thorax	**1.02 ± 0.10**	**0.43 ± 0.14**	**1.15 ± 0.12**	**U(1) = 5.60**	**0.0179**
Abdomen	0.51 ± 0.08	0.26 ± 0.13	0.56 ± 0.09	U(1) = 1.28	0.2586
Spine	0.41 ± 0.07	0.20 ± 0.11	0.45 ± 0.09	U(1) = 1.68	0.1952
Upper extremities	0.49 ± 0.06	0.37 ± 0.11	0.52 ± 0.07	U(1) = 0.32	0.5743
Lower extremities	0.70 ± 0.08	0.63 ± 0.15	0.72 ± 0.09	U(1) = 0.02	0.8838
External	0.57 ± 0.06	0.37 ± 0.10	0.61 ± 0.07	U(1) = 1.99	0.1579
Injury Severity Score	27.6 ± 0.88	24.4 ± 1.29	28.4 ± 1.03	U(1) = 2.38	0.1231
Pre-hospital events					
Apnea				**$\chi^2(2) = 12.2$**	**0.0023**
Yes	31 (16.3)	12 (34.3)	19 (12.3)		
No/Unknown	145 (76.3)	19 (54.3)	126 (81.3)		
Suspected	14 (7.4)	4 (11.4)	10 (6.5)		
Aspiration				TP(0) = 0.03	0.3467
Yes	5 (2.6)	2 (5.7)	3 (1.9)		
No/Unknown	155 (81.6)	27 (77.1)	128 (82.6)		
Suspected	30 (15.8)	6 (17.1)	24 (15.5)		
Cardiac arrest				TP(0) = 0.02	0.1387
Yes	17 (8.9)	3 (8.6)	14 (9.0)		
No/Unknown	167 (87.9)	29 (82.9)	138 (89.0)		
Suspected	6 (3.2)	3 (8.6)	3 (1.9)		
Hypotension				TP(0) = 0.05	0.6696
Yes	27 (14.2)	3 (8.6)	24 (15.5)		
No/Unknown	156 (82.1)	31 (88.6)	125 (80.6)		

Measure	Total (N=190)	Abuse		Analysis	
		Yes (N=35)	No (N=155)	Test statistic	p
Suspected	7 (3.7)	1 (2.9)	6 (3.9)		
Hypoxemia				$\chi^2(2) = 0.99$	0.6097
Yes	12 (6.3)	1 (2.9)	11 (7.1)		
No/Unknown	155 (81.6)	29 (82.9)	126 (81.3)		
Suspected	23 (12.1)	5 (14.3)	18 (11.6)		
Seizure				**$\chi^2(2) = 19.8$**	**<.0001**
Yes	22 (11.6)	10 (28.6)	12 (7.7)		
No/Unknown	150 (78.9)	18 (51.4)	132 (85.2)		
Suspected	18 (9.5)	7 (20.0)	11 (7.1)		
Hyperthermia				TP(0) = 0.18	0.1842
Yes	1 (0.5)	1 (2.9)	0 (0.0)		
No/Unknown	189 (99.5)	34 (97.1)	155 (100)		
Hypothermia				TP(0) < 0.01	0.0529
Yes	16 (8.4)	6 (17.1)	10 (6.5)		
No/Unknown	165 (86.8)	29 (82.9)	136 (87.7)		
Suspected	9 (4.7)	0 (0.0)	9 (5.8)		
Hyperventilation				TP(0) = 0.07	0.1792
Yes	6 (3.2)	2 (5.7)	4 (2.6)		
No/Unknown	182 (95.8)	32 (91.4)	150 (96.8)		
Suspected	2 (1.1)	1 (2.9)	1 (0.6)		

NOTE: TP indicates Fisher's exact test

Table 4

Resuscitation events and laboratory values by abusive head trauma

Measure	Total (N=190)	Abuse		Analysis	
		Yes (N=35)	No (N=155)	Test statistic	p
Complication					
Cardiac arrest	10 (5.3)	3 (8.6)	7 (4.5)	TP(0) = 0.18	0.3958
Hypotension	57 (30.0)	12 (34.3)	45 (29.0)	$\chi^2(1) = 0.38$	0.5402
Hypoxemia	7 (3.7)	2 (5.7)	5 (3.2)	TP(0) = 0.26	0.6146
Seizure	**26 (13.7)**	**11 (31.4)**	**15 (9.7)**	**TP(0) < 0.01**	**0.0020**
Hyperthermia	22 (11.8)	3 (8.8)	19 (12.4)	TP(0) = 0.21	0.7703
Hypothermia	48 (25.7)	13 (38.2)	35 (22.9)	$\chi^2(1) = 3.44$	0.0637
Hyperventilation	43 (23.0)	9 (26.5)	34 (22.2)	$\chi^2(1) = 0.28$	0.5944
Medication					
Anticonvulsant	72 (37.9)	15 (42.9)	57 (36.8)	$\chi^2(1) = 0.45$	0.5028
Hypertonic saline	78 (41.1)	17 (48.6)	61 (39.4)	$\chi^2(1) = 1.00$	0.3168
Mannitol	47 (24.7)	11 (31.4)	36 (23.2)	$\chi^2(1) = 1.03$	0.3097
Barbiturate	**12 (6.3)**	**6 (17.1)**	**6 (3.9)**	**TP(0) < 0.01**	**0.0104**
Fluids (ml/kg)					
In	56.7 ± 5.96	97.1 ± 25.2	47.6 ± 4.35	U(1) = 1.19	0.2755
Out	28.5 ± 4.50	56.0 ± 21.1	22.3 ± 2.60	U(1) < 0.01	0.9969
Labs					
Hemoglobin (g/dl)	**11.1 ± 0.15**	**9.78 ± 0.37**	**11.3 ± 0.15**	**t(183) = 4.16**	**<.0001**
Platelets ($x10^3$)	272 ± 7.47	288 ± 23.8	268 ± 7.51	U(1) = 0.29	0.5897
White blood cell	17.5 ± 0.54	17.2 ± 1.53	17.6 ± 0.57	t(175) = 0.24	0.8136
Sodium (meq/L)	141 ± 0.42	143 ± 1.41	141 ± 0.41	U(1) = 0.39	0.5298
Prothrombin time (sec)				$\chi^2(2) = 0.30$	0.8595
≥15	75 (39.5)	14 (40.0)	61 (39.4)		
<15	82 (43.2)	16 (45.7)	66 (42.6)		
Unknown/NA	33 (17.4)	5 (14.3)	28 (18.1)		
Partial thromboplastin time (sec)				$\chi^2(2) = 0.82$	0.6623

Measure	Total (N=190)	Abuse		Analysis	
		Yes (N=35)	No (N=155)	Test statistic	p
≥32	54 (28.4)	12 (34.3)	42 (27.1)		
<32	109 (57.4)	19 (54.3)	90 (58.1)		
Unknown/NA	27 (14.2)	4 (11.4)	23 (14.8)		
International normalized ratio				$\chi^2(2) = 2.69$	0.2599
≥1.5	35 (18.4)	4 (11.4)	31 (20.0)		
<1.5	124 (65.3)	27 (77.1)	97 (62.6)		
Unknown/NA	31 (16.3)	4 (11.4)	27 (17.4)		

NOTE: TP indicates Fisher's exact test

Table 5

Mortality measures by abuse

Measure	Total (N=190)	Abuse Yes (N=35)	Abuse No (N=155)	Analysis Unadjusted HR (95% CI)	Analysis p	Analysis Adjusted* HR (95% CI)	Analysis p
Died	38 (20.0)	9 (25.7)	29 (18.7)	1.470 (0.696–3.106)	0.3128	1.758 (0.209–14.77)	0.6033
Days to death	211 ± 172	161 ± 174	222 ± 170				
Cause of death							
System trauma	5 (13.2)	1 (11.1)	4 (13.8)				
Increased ICP	26 (68.4)	6 (66.7)	20 (69.0)				
Medical complications	2 (5.3)	0 (0.0)	2 (6.9)				
Other	5 (13.2)	2 (22.2)	3 (10.3)				
Other causes							
Diffuse axonal injury	1 (20.0)	1 (50.0)	0 (0.0)				
Hypoxic brain injury	1 (20.0)	0 (0.0)	1 (33.3)				
Intracranial hemorrhage	1 (20.0)	0 (0.0)	1 (33.3)				
Traumatic brain injury	2 (40.0)	1 (50.0)	1 (33.3)				

*Adjusted for age, sex, weight, cause and mechanism of injury, mode of transport to study hospital, Glasgow Coma Scale, international site, AIS thorax, pre-hospital apnea and seizure, seizure complications, barbiturate, hemoglobin, lowest systolic BP, highest heart rate, highest and lowest temperature, highest blood urea nitrogen, and highest creatinine