The association between lowest age-specific mean arterial pressure during the first four hours after pediatric intensive care unit admission and poor discharge outcome in pediatric traumatic brain injury

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Abstract

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The relation between mean arterial pressure and discharge outcome in children after severe traumatic brain injury is unclear. We assessed the prognosis of children with this condition in relation to the minimum age-specific mean arterial pressure percentile (ASMAPP) during the first four hours of intensive care unit admission. We examined the association between ASMAPP and discharge outcome in 168 pediatric patients admitted to the PICU with a Glasgow Coma Scale score < 9 who survived the first four hours of PICU admission. Poor discharge outcome was defined as in-hospital death, or discharge to an outside acute care facility or skilled nursing facility. Results were adjusted for non-head injury severity (maximum non-head abbreviated injury score (AIS) $\geq$ 3), head injury severity (head AIS $\geq$ 3), and vasoactive medication use within four hours of PICU admission. Data from 168 children with severe TBI were examined. Among children whose minimum ASMAPP exceeded the 4th percentile, the likelihood of an unfavorable outcome differed little across ASMAPP categories. In contrast, the proportions of patients with poor outcome (72%) or in-hospital death (67%) were high among those with minimum ASMAPP < 5th percentile. Compared to individuals with minimum ASMAPP > 75th percentile, those with a minimum ASMAPP < 5th percentile had a 60% increase in risk of a poor discharge outcome (95% confidence interval 0.8,3.2) and 3.8-fold increase in the risk of in-hospital death (95% confidence interval 1.3,11.4).

ASMAPP < 5th percentile within the first four hours of PICU admission for severe traumatic brain injury was strongly associated with in-hospital mortality.

Introduction:

Traumatic brain injury (TBI) is one of the leading causes of pediatric death and disability worldwide.[1] While the severity of the primary injury may decide outcome in some cases, many patients die from secondary injuries such as cerebral hypoxia, hypercarbia or increased intracranial pressure (ICP) that arise from injury cascades after severe TBI. [2] Hypotension after severe TBI has been identified as strongly associated with poor discharge outcomes in both children and adults.[3–5] As such, several organizations have published guidelines regarding appropriate levels of systolic blood pressure in children with TBI. [3–7] Mean arterial pressure (MAP) better approximates noncardiac organ perfusion than systolic blood pressure (SBP)[8,9], and MAP is one of the key components of the estimation of cerebral perfusion pressure (CPP) (by the formula CPP = MAP – intra cranial pressure (ICP)).[10] Management of CPP is cited by the Brain Trauma Foundation as one of the evidence-based guideline recommendations to improve outcomes for adults and children after severe TBI.[11] However, when an ICP monitor either has not been placed or cannot be placed, physicians may be forced to attempt to monitor cerebral perfusion pressure (CPP) in TBI patients by the observation of MAP with the assumption of a constant ICP. As such, understanding the discharge outcome associated with various MAP levels is of clinical importance.

Several studies have examined the association between systolic blood pressure and poor discharge outcomes in pediatric severe TBI [3–7,12] However, to date there have been no evaluations of the association between mean arterial pressure and discharge outcomes in pediatric traumatic brain injury. The aim of this study was to address this paucity of information by examining the prognosis of children with severe TBI in relation to the lowest age-specific mean arterial pressure percentile (ASMAPP) in the earliest hours of PICU admission.

Methods:

Study design and participants:

We undertook a cohort study by performing a secondary analysis of the Pediatric Guidelines Adherence and Outcome (PEGASUS) cohort.[13]

Study setting:

Harborview Medical Center is a 450-bed mixed level 1 adult and pediatric trauma hospital that serves the five-state Pacific Northwest region (Alaska, Idaho, Montana, Washington, and Wyoming). The 18-bed pediatric intensive care unit (PICU) admits approximately 120 children with traumatic brain injury annually. Patients are discharged from Harborview Medical Center to their home, Seattle Children's Hospital inpatient rehabilitation unit, a skilled nursing facility, or long-term acute care facilities. The University of Washington Institutional Review Board approved this study, with waiver of informed consent.

Study Participants:

Study participants were drawn from the 199 patients enrolled in the PEGASUS program.[13] Patients eligible for inclusion in the PEGASUS cohort were younger than 18 years with severe (Glasgow Coma Score (GCS) ≤ 8) traumatic brain injury (diagnosed by head CT) at any point during PICU stay. Eligible patients for this study were those who were alive as of four hours after PICU admission and were diagnosed with severe TBI at PICU admission.

Data Collection:

Data on demographic characteristics, injury severity and discharge outcomes were obtained from the Harborview Trauma Registry and clinical care documentation. Blood pressure values were obtained by Microsoft AMALGA from the electronic health record.

Mean arterial pressure:

SBP and diastolic blood pressure (DBP) were measured continuously at bedside via blood pressure cuffs throughout participants' time in the PICU. PICU nurses entered representative SBP and DBP hourly from admission to the PICU. SBP and DBP were mathematically transformed to MAP by the formula: MAP = DBP + 1/3 * (SBP-DBP).[14]

Age-specific mean arterial pressure percentiles (ASMAPP) for hospitalized pediatric patients were obtained from the age-specific mean arterial pressure quantiles laid out by Roberts et al.[15] To allow the creation of a continuous ASMAPP variable, z-scores were calculated for each age-group. Z-scores and population means were then utilized to determine the age-specific percentile for each MAP result. The lowest ASMAPP over the first four hours from PICU admission was chosen to increase the sensitivity of our study to detect lower ASMAPPs. For our primary analysis lowest ASMAPP was categorized into the groups: $<5^{th}$, 5^{th}-24^{th}, 25^{th}-49^{th}, 50^{th} – 74^{th} and $\geq 75^{th}$ percentile.

Outcome variable:

Discharge outcome was measured by discharge disposition obtained from the Harborview Trauma Registry. Discharge outcome was categorized as either “favorable” (discharge home or to an inpatient or outpatient rehabilitation service) or “unfavorable” (in-hospital death or discharge to a skilled nursing facility or outside acute care facility). In a second analysis we used in-hospital mortality as the outcome.

Data Analysis:

We used descriptive statistics to assess demographic and injury characteristics of the cohort stratified by discharge outcome. Univariate associations between potential confounders between MAP hypotension and discharge outcome were examined by chi-square analysis. We described the distribution of MAP per-patient by constructing histogram of the number of MAP values per patient over the first four hours from PICU admission. To examine the association between lowest ASMAPP over the first four hours from PICU admission and poor discharge outcome, we used unadjusted and adjusted Poisson regression with robust standard errors modeling ASMAPP as a categorical variable $<5^{th}$, 5^{th}-24^{th}, 25^{th}-49^{th}, 50^{th} – 74^{th} and $\geq 75^{th}$. $> 75^{th}$ percentile will be used as the referent for our analysis as previous studies have identified this group as having the lowest proportion of poor discharge outcome.[6,7]. We repeated the above analysis using in-hospital death as the outcome of interest. All statistical analyses were performed with R version 3.5.3.

Results:

Participants:

Of the 199 patients in the initial PEGASUS cohort, 175 were admitted to the PICU with severe TBI. Of these, 168 (96%) survived the first four hours from PICU admission. Demographic information and clinical characteristics for the overall cohort and stratified by discharge outcome are presented in Table 1. Patients were primarily male (n = 117, 69.6%). The most common mechanism was motor vehicle collision (n = 55, 32.7%). Median [IQR] admission Glasgow Coma Score (GCS), and admission GCS motor score were 6 [3, 7] and 1 [1, 1], respectively.

Outcome data:

Of the 168 patients admitted to the PICU with severe TBI who survived four hours from PICU admission, 52 (31%) had poor discharge outcomes and 30 (18%) died within the hospital. Compared to those with favorable discharge, patients with poor discharge outcome were younger (median [IQR] 7.1 [2.0, 15.4] vs. 13.4 [4.7, 16.0] years).

Exposure data:

The number of MAP values obtained in the first four hours of PICU admission is presented in Figure 1. The median [IQR] number of values per patient was 5 [3, 8]. Median [IQR] minimum age-specific mean arterial pressure percentile was 40% [16%, 69%].

Statistical Analyses

The lowest proportion of poor discharge outcome occurred in children with minimum ASMAPP between the 50^{th} and 74^{th} percentile (15.2% 95% CI (0%, 30%). The highest proportion of poor discharge outcome occurred in children with minimum ASMAPP < 5^{th} percentile (72% 95%CI (52%, 93%)). The number of patients in each minimum ASMAPP group stratified by discharge outcome and their adjusted and unadjusted risk relative to the referent group are presented in Table 3. The risks of poor discharge adjusted for vasoactive medication use, head injury severity, and non-head injury severity for each of the percentile groups relative to the referent category of >75^{th} percentile (aRR (95%CI)): <5^{th}: 1.6 (0.8 , 3.2), 5^{th} – 24^{th}: 0.9 (0.4, 1.8), 25^{th} – 49^{th}: 0.9 (0.4, 1.7), 50^{th}- 74^{th}: 0.5 (0.2, 1.3).

When utilizing in-hospital death as the outcome the group with the lowest proportion of death was also the 50^{th}-74^{th} group (9.1%, 95% CI (0.0, 18.9%)). The group with the highest proportion of in-hospital death was <5^{th} percentile (67% CI (45%, 88%)). The risks of in-hospital mortality adjusted for vasoactive medication use, head injury severity, and non-head injury severity for each of the percentile groups relative to the referent category of >75^{th} percentile (aRR): <5^{th}: 3.8 (1.3 , 11.4), 5^{th} – 24^{th}: 1.1 (0.4, 3.5), 25^{th} – 49^{th}: 0.7 (0.2, 2.4), 50^{th}- 74^{th}: 0.7 (0.2, 2.7).

Discussion

Hypotension after severe pediatric traumatic brain injury has been documented by several studies as being predictive of a poor prognosis.[3–7] However, hypotension has historically been defined by systolic blood pressure, which does a poorer job of approximating noncardiac organ perfusion than mean arterial pressure. In the setting of severe traumatic brain injury, where cerebral perfusion pressure is defined by the difference of mean arterial pressure and intracranial pressure, understanding the relationship between hypotension as defined by mean arterial pressure and poor discharge outcomes is of clinical importance. To the best of our knowledge, this is the first study examining the association between mean arterial pressure and discharge outcomes in pediatric severe TBI. The main finding of this study is that minimum MAP < 5th percentile within the first four hours of PICU admission was associated with increased risk of in-hospital mortality.

Management of cerebral perfusion pressure is one of the core principles guiding the management of pediatric severe traumatic brain injury.[11] However, in the period of time where intracranial pressure monitors either have not been placed or cannot be placed, physicians may be forced to monitor CPP indirectly through MAP with the assumption of a static intracranial pressure. Furthermore, impaired cerebral autoregulation is common in pediatric severe TBI.[16] Cerebral autoregulation is typically able to mitigate decreases in CPP by inducing vasodilation which decreases ICP thus stabilizing CPP. When this homeostatic mechanism is disrupted decreases in mean arterial pressure can result in decreases in CPP which can cause ischemia resulting in exacerbation of secondary injury. This study identifies an association between lowest age-specific mean arterial pressure and in-hospital mortality in pediatric patients with severe TBI in a period of PICU admission where ICP monitors were unlikely to be available to physicians. As such, these findings may be of important prognostic value to physicians during the management of severe TBI.

There have been no studies examining the association between ASMAPP and poor discharge outcomes in pediatric TBI. However, two studies have examined the association between age-specific systolic blood pressure percentiles and discharge outcomes in TBI. Suttipongkaeset et al examined the association between hospital admission systolic blood pressure percentiles (categorized as <5th, 5th-24th, 25th – 74th, 75th – 94th, >95th), and in-hospital mortality and found that SBP < 5th percentile had the highest proportion of in-hospital death with a case-fatality of 66.3 % (62.7, 69.7%). In Vavilala et al, poor discharge outcome (as defined by Glasgow outcome scale < 4) was highest among Emergency Department admission SBP percentile < 5th percentile (Compared to the categories of 5th - 24th, 25 – 74th, 75th – 89th, 90 – 94th and ≥ 95th). Both studies identified that mortality decreased sharply once age specific SBP percentile was ≥ 5th percentile and continued to decrease until the 75th percentile. Our findings suggest that a MAP < 5th percentile by age also is associated with in-hospital mortality in pediatric severe TBI.

Limitations:

There are several important limitations to this study. First, given an inability to abstract information from pre-hospital records we have a poor ability to control for potential confounders arising from pre-PICU arrival (time since injury, pre-hospital treatments, etc). Second, potentially important in-hospital confounders of the relationship between mean arterial pressure and poor discharge outcome such as temperature, coagulation, blood gas data, cerebral autoregulation and glucose were not collected. Furthermore, early administration of sedative medications to facilitate tracheal intubation could depress MAP and be associated with adverse discharge outcomes. Finally, while discharge outcome has been associated with long term morbidity post TBI, having Glasgow Outcome Scores at 3 and 6 months would represent a superior measure of long-term morbidity. Finally, our results are generalizable only to those children who survive the first four hours of PICU admission.

Conclusion:

Lowest age-specific mean arterial pressure percentile < 5th percentile within the first four of PICU admission was associated with high risk of in-hospital mortality after severe TBI in children.

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Table 1: Clinical characteristics of PEGASUS program participants (May 2011 - July 2017) admitted with severe TBI who survived the first 4 hours from PICU admission (n = 168)

	Overall n = 168	Poor discharge outcome N = 52	Favorable discharge outcome N = 116
Age (years), mean (range)	9.9 (< 1 month – 17.9)	10.6 (6 months – 17.9)	8.4 (<1 month – 17.6)
Males, n (%)	117 (69.6)	35 (67.3)	82 (70.7)
Mechanism of TBI, n (%)			
Motor vehicle crash	55 (32.7)	15 (28.8)	40 (34.5)
Fall	40 (23.8)	8 (15.4)	32 (27.6)
Struck by vehicle	36 (21.4)	9 (17.3)	27 (23.3)
Abusive TBI	12 (7.1)	11 (21.2)	1 (0.9)
Sport or recreation	14 (8.3)	3 (5.8)	11 (9.5)
Gunshot	10 (6.0)	6 (11.5)	4 (3.4)
Other	1 (0.6)	0 (0.0)	1 (0.9)
GCS score by EMS, median [IQR]	3.0 [3.0, 7.3]	3.0 [3.0, 5.0]	3.5 [3.0, 8.3]
Pediatric Trauma Score, median [IQR]	3.0 [2.0, 5.0]	2.0 [0.8, 3.0]	4.0 [2.0, 6.0]
Transport type, n (%)			
Ambulance	66 (39.3)	20 (38.5)	46 (39.7)
Helicopter	51 (30.4)	15 (28.8)	36 (31.0)
Fixed wing aircraft	50 (29.8)	17 (32.7)	33 (28.4)
Personal vehicle	1 (0.6)	0 (0.0)	1 (0.9)
Advanced life support transport, n (%)	14 (8.3)	3 (5.8)	11 (9.5)
Prehospital tracheal intubation, n (%)	168 (100.0)	52 (100.0)	116 (100.0)
Vasoactive medication use, n (%)	13 (7.7)	12 (23.1)	1 (0.9)
GCS score on admission to ED, median [IQR]	6.0 [3.0, 7.0]	3.0 [3.0, 5.8]	6.0 [3.0, 7.0]
GCS score on admission to PICU, median [IQR]	7.0 [4.8, 10.0]	4.0 [3.0, 6.0]	9.0 [7.0, 11.0]
GCS motor score in ED, median [IQR]	1.0 [1.0, 1.0]	1.00 [1.0, 1.0]	1.0 [1.0, 1.0]
GCS motor score at discharge, median [IQR]	6.0 [6.0, 6.0]	4.5 [3.0, 6.0]	6.0 [6.0, 6.0]
AIS head score, median [IQR]	5.0 [4.0, 5.0]	5.0 [5.0, 5.0]	4.0 [4.0, 5.0]
Highest AIS non-head score, median [IQR]	2.0 [1.0, 3.0]	3.0 [1.0, 4.0]	2.0 [1.0, 3.0]
Injury Severity Score, median [IQR]	30.00 [23.5, 38.0]	34.5 [26.0, 45.0]	27.0 [21.0, 34.0]
Polytrauma, n (%)	73 (43.5)	27 (51.9)	46 (39.7)
Any surgery, n (%)	106 (63.1)	27 (51.9)	79 (68.1)
Craniotomy, n (%)	47 (28.0)	14 (26.9)	33 (28.4)
Intracranial pressure monitoring, n (%)	63 (37.5)	19 (36.5)	44 (37.9)
No brain herniation	61 (36.3)	29 (55.8)	32 (27.6)
Avoidance of unwanted hypocarbia, n (%) *	66 (71.7)	12 (60.0)	54 (75.0)
Maintenance of all CPP, n (%)	107 (63.7)	21 (40.4)	86 (74.1)
Early initiation of nutrition, n (%)	139 (82.7)	29 (55.8)	110 (94.8)

AIS=Abbreviated Injury Scale. CPP=cerebral perfusion pressure. ED=emergency department. EMS=emergency medical services. GCS=Glasgow Coma Scale. PICU=pediatric intensive care unit. TBI=traumatic brain injury. *In patients without brain herniation. IQR = interquartile range

Table 2: Association between minimum age-specific mean arterial pressure percentile over the first four hours from PICU admit and poor discharge disposition and in-hospital death among PEGASUS participated admitted to the pediatric intensive care unit with severe traumatic brain injury, and survived four hours from PICU admission (N = 168).

Minimum age-specific mean arterial pressure percentile	Number of patients by discharge outcome		Relative risk (95% confidence interval) of poor discharge outcome		Number of patients by survival status		Relative risk (95% confidence interval) of death	
	Poor	Favorable	Unadjusted	Adjusted	Died	Survived	Unadjusted	Adjusted
< 5th	13	5	2.3 (1.4,4.1)	1.6 (0.8,3.2)	12	6	5.2 (2.2,12.6)	3.8 (1.3,11.4)
5th - 24th	11	24	1 (0.5,2)	0.9 (0.4,1.8)	6	29	1.3 (0.4,4)	1.1 (0.4,3.5)
25th - 49th	11	32	0.8 (0.4,1.7)	0.9 (0.4,1.7)	4	39	0.7 (0.2,2.5)	0.7 (0.2,2.4)
50th - 74th	5	28	0.5 (0.2,1.3)	0.5 (0.2,1.3)	3	30	0.7 (0.2,2.7)	0.7 (0.2,2.7)
≥ 75th	12	27	Referent	Referent	5	34	Referent	Referent

*Analyses adjusted for severe head injury (Head AIS > 3, Binary), severe non-head injury (maximum non-head AIS > 3, binary) and vasoactive use within the first four hours of PICU admission (Y/N)

Figure 1: Histogram of the number of mean arterial pressure values collected per patient in the first 4 hours of PICU admission (n = 168).