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Admission hyperglycemia is a reliable outcome predictor in children with severe traumatic brain injury

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Abstract

Objective: To identify the relationship between admission hyperglycemia and outcome in children with severe brain injury at hospital discharge and 6 months later.

Method: A retrospective analysis of blood glucose levels was conducted in 61 children with severe brain injury admitted to the Pediatric Intensive Care Unit between November 1, 2005 and October 30, 2009. Hyperglycemia was considered for a cut off value of > 150 mg/dL, based on literature. Outcome was measured with the Glasgow Outcome Scale at hospital discharge and 6 months after discharge. Death was also analyzed as an outcome measure.

Results: Mean admission blood glucose of the patients was 251 mg/dL (68-791). Hyperglycemia was noted on admission in 51 (83.6%) patients. A moderately significant positive correlation was found between admission blood glucose and severity of head trauma according to Abbreviated Injury Score ($r = 0.46$). Mean admission glucose level of non-survivors was significantly higher (207 mg/dL vs. 455 mg/dL, $p < 0.001$). Mean blood glucose level of the patients in bad outcome group was found significantly higher compared to that of the patients in good outcome group at hospital discharge and 6 months after discharge (185 mg/dL vs. 262 mg/dL, $p < 0.05$ and 184 mg/dL vs. 346 mg/dL, $p < 0.05$, respectively).

Conclusions: Hyperglycemia could be considered as a marker of brain injury and, when present upon admission, could reflect extensive brain damage, frequently associated with mortality and bad outcome. Further studies are needed to investigate the effect of strict glycemic control on mortality and outcomes.

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Introduction

Traumatic brain injury (TBI) is the major cause of mortality among children, and leads to significant morbidity among survivors. Although injuries related to trauma are the main cause of early deaths, conditions that develop following trauma, such as hypoxia, hypotension, increased intracranial pressure, and hyperglycemia, increase mortality.[1-3] Thus, prevention and early treatment of pathologies that could lead to secondary injuries are considered to improve outcomes. Despite aggressive treatments, many of the survivors of severe TBI have lasting neurological, psychological and social developmental deficits. Over the past several years, important research has sought to better understand these deficits and to improve the outcome for children. Hyperglycemia in trauma victims has been associated

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with multiple trauma, significant TBI, low Glasgow Coma Scale (GCS), and poor neurological outcome. Both adult and pediatric trauma literature evaluate the relationship of hyperglycemia to outcomes after head injury. An unambiguous association exists between hyperglycemia, severity of head injury, and outcome from traumatic head injury in adult patients.[4,5] In children, however, the impact of hyperglycemia on outcomes is less apparent, and the direct consequences of hyperglycemia and therapeutic interventions to control blood glucose level on outcome remain unknown. The aim of this retrospective study was to identify the relationship between admission blood glucose of the patients who were admitted to the Pediatric Intensive Care Unit (PICU) due to severe head trauma and mortality, outcomes at hospital discharge and 6 months later, and severity of the trauma.

Methods

In this single-center study, medical records of the patients who were under 18 years of age and were admitted to the PICU of Ondokuz Mayıs University Medical Faculty between November 1, 2005 and October 30, 2009 due to severe head trauma, defined by an initial GCS ≤ 8, were analyzed retrospectively. We excluded patients without a documented blood glucose value at the time of admission, and then completed chart reviews of the identified and included patients. None of these children received intravenous infusion of glucose or steroid therapy, and none had a previous history of diabetes mellitus or endocrine disease, according to family's information contained in medical files. Blood sample was taken from the peripheral vein in our emergency department at admission, and levels of blood glucose measured in blood samples were recorded. Hyperglycemia was considered for a cut-off value of > 150 mg/dL, and hypoglycemia was considered for a cut-off value of < 60 mg/dL, based on literature.[6] When blood glucose level was > 180 mg/dL, insulin treatment was started according to our PICU hyperglycemia protocol. Demographic features of the patients, causes of head trauma, accompanying traumas to head trauma, intubation, number of days on mechanical ventilation, length of PICU stay, and mortality were recorded. Trauma and mortality scores on admission were calculated from medical records of the patients. We selected Glasgow Outcome Scale (GOS) score as a standard outcome measure. GOS scores of survivor patients were calculated at hospital discharge and 6 months after discharge using medical records. Patients were divided into two groups as good outcome group (GOS score of 4-5) and bad outcome group (GOS score of 1-3). Death was also analyzed as an outcome measure.

Statistical analysis was done using SPSS 15 (Statistical Package for the Social Sciences, version 15) for Windows. Data were given as median (minimum-maximum) and number (percentage), unless otherwise specified. Mann-Whitney U test was used for intergroup comparisons. Relationship between Abbreviated Injury Score (AIS) and blood glucose level was analyzed with Spearman's rank correlation test. Statistical significance was defined as $p < 0.05$. Approval of local ethics committee was obtained prior to the study.

Results

A total of 65 patients were admitted to PICU due to severe head trauma between November 1, 2005 and October 30, 2009. Four patients who abandoned follow up after hospital discharge were excluded. Of the 61 patients who constituted the study group, 19 (31%) were girls and 42 (69%) were boys, with a mean age of 48 months (3 months-18 years). When causes of head trauma were analyzed, in-car traffic accident was found in 17 patients (28%), out-car traffic accident was found in 19 patients (31%), and falls were detected in 25 patients (41%). While 22 patients (36%) had isolated head trauma, multiple trauma was detected in 39 patients (64%) along with head trauma. Forty-five (73.8%) patients required endotracheal intubation and mechanical ventilation. While mean duration of mechanical ventilation was 4 days (1-13), mean PICU length of stay was 5 days (1-120). Of the 61 patients, 14 died, yielding a mortality rate of 23%. Demographic characteristics and trauma and mortality scores of the patients are seen in Table 1. Severity of head trauma according to AIS varied between 3 and 6 (Table 2). Outcomes of the 47 survivor patients who were discharged were assessed according to GOS at hospital discharge and 6 months after discharge. Twenty patients (42.5%) had good outcomes and 27 patients (57.5%) had bad outcomes at discharge. After 6 months, 37 patients (78.7%) had good outcomes and 10 patients (21.3%) had bad outcomes.

Mean admission blood glucose of the patients was 251 (68-791) mg/dL. Hyperglycemia was detected on admission in 51 patients (83.6%). Hypoglycemia was detected in none of the patients. A moderately significant positive correlation was found between admission blood glucose and severity of head trauma according to AIS ($r = 0.46$); that is, mean admission blood glucose level increased as severity of head trauma according to AIS increased (Table 2). The patients were divided into two groups which consisted of 47 survivors and 14 non-survivors, and the groups were compared in terms of admission blood glucose. The mean admission glucose level of non-survivors was significantly higher (207 mg/dL vs. 455 mg/dL, $p = 0.001$) (Table 3). At hospital discharge, good outcome (n = 20, 42.5%) and bad outcome (n = 27, 57.5%) groups were compared in terms of admission blood glucose, and mean glucose level of the patients in bad outcome group was found to be significantly higher (185 mg/dL vs. 262 mg/dL, $p = 0.015$).

Table 1 - Demographic characteristics and trauma and mortality scores of the patients

Variables	Patients (total = 61)
Age (months), median (minimum-maximum)	48 (3 months-18 years)
Gender, n (%)	
Boy	42 (69)
Girl	19 (31)
Causes of trauma, n (%)	
In-car traffic accident	17 (28)
Out-car traffic accident	19 (31)
Fall	25 (41)
Isolated head trauma, n (%)	22 (36)
Multiple trauma, n (%)	39 (64)
MV, n (%)	45 (73.8)
MV duration*, mean	4 (1-13)
PICU length of stay*, mean	5 (1-120)
Mortality, n (%)	14 (23)
Trauma and mortality scores	
GCS	7 (3-8)
ISS	25 (9-75)
RTS	4.59 (0.01-7.48)
TRISS	68% (1.8-99.6)
PRISM	20.5 (0-64)

GCS = Glasgow Coma Score; ISS = Injury Severity Score; MV = mechanical ventilation; PICU = pediatric intensive care unit; PRISM = Pediatric Risk of Mortality; RTS = Revised Trauma Score; TRISS = Trauma and Injury Severity Score.
* In days.

Table 2 - Relationship between blood glucose levels and severity of head trauma according to AIS

AIS	n	Blood glucose (mg/dL)*
3	13	182 (110-313)
4	37	269 (93-791)
5	6	429 (68-583)
6	1	151

AIS = Abbreviated Injury Score.
* Mean (range).

Six months later, mean admission blood glucose level of the patients in bad outcome group (n = 10, 21.3%) was also significantly higher compared to that of the patients in good outcome group (n = 37, 78.7%) (184 mg/dL vs. 346 mg/dL, p = 0.04) (Table 3).

Table 3 - Relationship between blood glucose levels and mortality and outcomes

Level	Mortality/outcomes	p
Blood glucose, mean (mg/dL)		0.001
Survivors (n = 47)	207 (93-584)	
Non-survivors (n = 14)	455 (68-791)	
Discharge		
Blood glucose, mean (mg/dL)		0.015
Good outcome (n = 20)	185 (105-377)	
Bad outcome (n = 27)	262 (93-584)	
6 months after discharge		
Blood glucose, mean (mg/dL)		0.04
Good outcome (n = 37)	184 (105-570)	
Bad outcome (n = 10)	346 (93-584)	

Discussion

Prevalence of hyperglycemia due to head trauma is considered to be high in the published literature.[3,6,7] Pathophysiology of hyperglycemia is not fully understood, although various hypotheses have been suggested. The causes of such condition are reported to be multifactorial and related to posttraumatic stress response. Abrupt metabolic response to injury could include major changes in the levels of circulating cortisol, glucagon, and epinephrine, resulting in impaired metabolism of glucose associated with insulin resistance, high blood and tissue glucose levels, intracellular acidosis, lactate accumulation, energetic failure, and, consequently, neuronal injury.[2,3] Distinguishing the cause-and-effect relationship between hyperglycemia and poor outcome after TBI remains difficult. Many authors have implied that hyperglycemia may reflect the extent of TBI.[4,5,8] However, many studies have also shown that hyperglycemia exacerbates the impact of ischemia and hypoxia, ultimately resulting in worse outcomes after a variety of insults.[9,10]

The results of our study confirm prior research demonstrating an association between poor neurologic outcome and elevated admission blood glucose levels after TBI in children.[2,4,6,11,12] In the study of Cochran et al., admission blood glucose of > 300 mg/dL was found related to increased mortality and bad outcomes according to GOS in children with head trauma.[2] In the study that Chiaretti et al. carried out with 122 pediatric patients with severe head trauma, the authors reported a significant relationship between admission blood glucose and bad outcomes according to GOS at hospital discharge.[4] Similarly, hyperglycemia on admission was reported to be associated with mortality and bad outcomes at discharge and after 6 months in the study of Melo et al.[12] The study by Rovlias

& Kotsou, however, included only adult patients, and determined that postoperative glucose was an independent predictor of outcome.[5] In our study, hyperglycemia on admission was also associated with severity of trauma, mortality and bad outcomes on hospital discharge. Admission hyperglycemia was associated with bad outcomes 6 months after discharge in our study, similarly to the results of the study of Melo et al., which is unique in literature investigating the outcomes of hyperglycemia 6 months after discharge in children with severe TBI.[12]

Previous studies have used different glucose values to define hyperglycemia in the context of pediatric TBI. These values vary and range from 150 mg/dL to as high as 270 mg/dL.[4,5] However, the treatment threshold for hyperglycemia is controversial in both adults and children; some clinicians may not administer insulin for a glucose of 150 mg/dL for fear of hypoglycemia, and others may consider a glucose of 270 mg/dL to be too high a treatment threshold. In a randomized, controlled study involving more than 1,500 critically ill adults, van den Berghe et al. recommended intensive insulin therapy to maintain blood glucose ≤ 110 mg/dL, in order to reduce morbidity and mortality.[13] Despite the evidence for an association between hyperglycemia and worsened outcome in PICU, glycemic control has not been evaluated in critically ill children.[14] Parish & Webb argued against insulin treatment of hyperglycemic head-injured children, because most children in their series experienced only a transient hyperglycemia.[7] In the study of Melo et al., the authors detected that blood glucose returned to normal spontaneously 48 hours after the trauma in 75% of the patients who were hyperglycemic on admission. However, they compared the outcomes of these patients according to GOS with those whose hyperglycemia continued 48 hours later, and they indicated that outcomes were significantly better among the first group of patients.[12]

In conclusion, admission hyperglycemia was associated with severity of trauma, mortality and bad outcomes both at hospital discharge and 6 months after discharge in our study. Further studies are needed to investigate the effect of strict glycemic control on mortality and outcomes in pediatric patients with head trauma.

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