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Evaluation of Blood Glucose and Inflammation Markers in Pediatric Head Injuries

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ABSTRACT

The aim of this study was to investigate the relationship between early (at the first admission to the emergency room) blood glucose, C-reactive protein (CRP) and leukocyte (WBC) levels and Glasgow Coma Scale (GCS) in patients with pediatric isolated head injury (IHI) and to reveal their effects on prognosis in the emergency department.

The data of 74 patients with IHI under the age of 18 and over the age of 2, admitted to Kars Harakani State Hospital Emergency Department between 2016 and 2019, were obtained from the hospital information system and analyzed retrospectively.

It was reported that 54 of our patients were boys and 20 were girls. Concerning injury etiology, it was determined that 21.6% were exposed to head injury due to a traffic accident, 59.4% due to falling, 9.5% due to battery, and the same percentage due to a foreign body hit on the head. According to the severity of brain damage, 65 patients with the GCS score above eight and 9 patients with the GCS score below and equal to eight were identified. While a significant negative correlation was found between the GCS scores and blood glucose and WBC levels of our patients, the difference between the CRP levels was found to be insignificant.

In children with pediatric IHI, a negative correlation was found between increased blood glucose and WBC levels and GCS score in the early period in predicting the severity of damage in addition to computerized brain tomography (CBT), and it was associated with poor prognosis in the emergency department.

Key Words: Pediatric Isolated Head Injury, Glucose, WBC, CRP, GCS score

Introduction

When the causes of mortality and morbidity in the child age group around the world are examined, head injuries (TBI) rank third (1). In Turkey, it is reported that the most common causes of death within the 0-14 age group are due to injury and poisoning (2). Among the etiologies of pediatric injuries, motor vehicle accidents, child abuse, and falls are the most common causes (3).

Glasgow Coma Scoring (GCS) is the gold standard method in the evaluation of neurological status in patients with head injury (4). However, since there may be different examination findings in sound stimulus response in the pediatric patient group compared to adults, modified scoring systems are also used (5). While the head injury is considered to be mild if a patient's GCS score is 14-15, a GCS score of 9-13 is considered to be a moderate head injury, and a GCS score of ≤ 8 is considered to be a severe head injury (6). Skull fractures constitute a significant part of closed head injuries in pediatric patients (7). Linear fractures constitute approximately 75% of skull fractures in children and are frequently observed in the parietal region as a location (8). Although there are many imaging methods in the diagnosis of skull injuries, computerized brain tomography (CBT) is still used as the first choice since it is both non-invasive and fast. Furthermore, CBT also allows for the detection of pathologies that occur secondary to injury in the parenchyma and bone (9). The prognosis and clinical course of head injuries in childhood are better compared to adults. The school period and toddler period children constitute the group with a high mortality rate. The main purpose of approaching head injuries in children is to maintain cerebral functioning, to prevent herniation, to provide electrolyte balance, and to prevent a secondary injury (10).

In addition to the clinical and radiological findings of the disease, laboratory findings are also helpful in shaping the diagnosis and treatment in pediatric isolated head injuries (IHI) as in many diseases. Although mechanisms involving biochemical changes (hypermetabolic, hypercatabolic changes and increases in various acute-phase proteins due to the acute-phase response) have been well documented in adult patients with a severe head injury, hemodynamic mechanisms are not clear in pediatric severe IHI. Furthermore, the limited number of studies

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examining the relationship between blood parameters and GCS scores in pediatric patients, and different opinions in the studies that reveal the effect of blood parameters on the prognosis of the disease have caused researchers to conduct more studies in this regard.

In the study, early blood glucose, WBC and CRP levels were investigated in pediatric patients diagnosed with IHI, and the biochemical mechanisms underlying the disease were investigated. Furthermore, differences and correlations in blood parameters according to patients' GCS scores were examined, and it was aimed to reveal their effects on prognosis in the emergency department.

Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki, and the ethical approval dated 03.04.2019 was obtained from the Local Ethics Committee of Kafkas University Faculty of Medicine before starting the study (No: 2019-90-05). From among the patients with IHI who were admitted to Kars Harakani State Hospital Emergency Department between 01.01.2016 and 01.04.2019 and evaluated by a neurosurgeon, the data of 74 patients who met the criteria of being under the age of 18 and over the age of 2 were analyzed retrospectively. Patients under the age of eighteen and over the age of two, with a history of multiple trauma, without follow-up and available data, and with any medical treatment before applying to the emergency department were excluded from the study. Moreover, all infection conditions that might change the glucose value in the blood and increase leukocyte and CRP levels, cancers, having a history of recent surgery, having a history of endocrine disease, and the conditions such as being under hormone or drug therapy were determined as the exclusion criteria of our study. The Pediatric Emergency Care Applied Research Network (PECARN) prediction rules were used to evaluate clinically significant head injuries with severe injury mechanisms (11). The patients were examined in terms of age, gender, admission complaint, the history of injury, injury localization, laboratory parameters, treatments administered, follow-up periods and complications. Since retrospective data were used in our study, there was no need to obtain an informed consent form, and patients' data were kept confidential.

Pediatric patients were classified according to the etiology of IHI as a traffic accident, falling, battery, and foreign body hit on the head. Head injuries caused by sports injuries and battery were excluded from the study without being included in any reliable group since inconsistencies were found in patients' epicrises.

The GCS score was subclassified as the GCS score of 14-15 (mild head injury), GCS score: 9-13 (moderate) and GCS score: 3-8 ($\leq$ 8 severe) in order to show the severity of brain damage in patients. To show the relationship between blood parameters and brain damage in the study, while individuals with the GCS score above eight in the general analysis were designed to represent mild-moderate brain damage, the group with the GCS score of eight and equal to eight was designed to represent the presence of severe brain damage (12). The biochemical parameters tested here were glucose, WBC, neutrophil (NEU) and CRP. Furthermore, these routine biochemical and hemogram tests in the study represent the initial blood values of patients at the time of admission to the emergency department. Patients who were admitted only to the intensive care and neurosurgery department from the emergency department represented poor prognosis (mortality could not be included in the poor prognosis since there was a deceased patient), and discharge with full recovery from the emergency department represented good prognosis. The complete blood count analysis was performed using a flow cytometric method with an ABX-Pentra DX 120 (Horiba LTD, Japan) device. Serum CRP analysis was performed using the immune-turbidimetric method and, glucose analysis was performed using photometric method with a Cobas C501 (Roche Diagnostic, Germany) device. Reference assay ranges of the analytical methods used are; WBC: 3.7-10.4 x10^3/µL, NEU: 1.8-7.8 x10^3/µL, glucose: 70-100 mg/dL, CRP: 0-0.5 mg/dL.

All statistical analyses of the research data were performed using the IBM SPSS 22.0 program. The Kolmogorov-Smirnov analysis was performed to determine the suitability of the continuous (quantitative) variables to normal distribution indicated by measurement. The relationship between the etiologies of injuries by age, one of the categorical variables of the patients, was determined by Fisher's exact test, and other categorical variables (age, gender, the presence of symptoms and brain CT results, indication for surgical operation) were given as descriptive statistics. The correlation between the rate of admission to the intensive care unit and the GCS score was evaluated, and the relationships of blood parameters with GCS score and prognosis were evaluated. There were Pearson's correlation analysis was used for data conforming to normal distribution, and Spearman's correlation analysis was used to show the relationship between data that did not pass the normality test. In addition, the differences between blood parameters in the GCS subgroups was evaluated by the Mann-Whitney U test. Our study sample included all patients with pediatric IHI whose data were accessible. A p-value less than 0.05 ($p<0.05$) was considered as the lowest value of significance in all tests. The means between the groups were given as median (min-max).

Results

In the study, the total number of patients who met the appropriate criteria and were analyzed retrospectively was 74. It was reported that 54 (73%) of our patients were boys and 20 (27%) were girls (Table 1).

When the etiologies of head injuries that occurred in our patients in the school period (period over the age of five) were investigated, it was determined that while 14 (26.9%) of our patients were exposed to head injury due to a traffic accident, 27 (51.9%) of them were exposed to it due to falling, 7 (13.5%) of them were exposed to it due to battery, and 4 (7.7%) of them were exposed to it due to a foreign body hit on the head. During the toddler period (the period between the age of 2-5 years), these rates consisted of 17 (77.3%) fallings, 3 (13.6%) foreign body hits on the head, and 2 (9.1%) traffic accidents, and no battery case was found in this age group (Table 2). According to the statistical analysis revealed in terms of the way of exposure to injury during the school and toddler periods, the rate of observing head injuries due to "falling" was statistically significant and high in the toddler period group ($p=0.02$) (Table 2).

According to the patients' CBTs, it was reported that while 29 (39.1%) of the localizations of head injuries were in the frontal region, 12 (16.2%) of them were in the occipital region, 16 (21.7%) of them were in the parietal region, and 17 (23%) of them were in the temporal region (Table 3). When the pathologies of head injuries were evaluated, it was observed that there was subdural hemorrhage by 12.1%, epidural hemorrhage by 25.6%, subarachnoid hemorrhage (SAH) by 13.5%, contusion by 19%, and cranial bone fracture by 29.8% (Table 3).

Furthermore, it was investigated whether there was an indication for surgical treatment applied according to the type of hemorrhage in patients. Since there was no death in hospitalized patients, its effect on mortality could not be revealed (Table 4).

When the GCS scores divided into subgroups for the evaluation of patients' brain damage were examined, it was determined that 50 (67.6%) patients had the GCS score of between 14-15 (mild head injury) and 15 patients (20.3%) had the GCS score of between 9-13 (moderate), on the other hand, the remaining nine patients (12.1%) were found to have the GCS score of 3-8 (≤ 8 severe), and in this group, there was one patient who died in the emergency department and this patient's GCS score was 3. In total, there were nine patients in the group with the GCS score of eight and below eight, and there were 65 patients in the group with the GCS score of above eight (Table 5). While 39 patients with the GCS above 8 on the first arrival to the emergency department were discharged from the emergency department, 13 patients were hospitalized in the neurosurgery department. While 8 (100%) of a total of 21 patients hospitalized in intensive care had the GCS score of 8 and below, it was determined that 13 (20%) of them had the GCS score above 8. A negative correlation was observed between the rate of admission to the intensive care unit and GCS score ($r=-0.40$, $p=0.045$). Furthermore, while all hospitalized patients (in the intensive care unit and neurosurgery department) were discharged with full recovery and current state, the relationship between the GCS score and discharge from the emergency department was found to be significant ($p=0.029$).

When the differences between blood values in the patients' GCS subgroups was examined, it was determined that the WBC and glucose values of individuals with the GCS score of ≤ 8 were significantly higher ($p<0.05$ for WBC; $p<0.01$ for glucose) compared to individuals with the GCS score of > 8 (Table 5). Additionally, the difference between the CRP levels between the two subgroups was found to be insignificant.

When the relationship of blood parameters with GCS and prognosis is examined, it was determined that WBC values were negatively correlated ($r=-0.49$, $p=0.038$) with patients with the GCS score of eight and below, and positively correlated with poor prognosis in the emergency department (hospitalization rates) ($r=0.48$, $p=0.04$). A positive correlation was observed between high WBC values and increases in NEU ($r=0.80$, $p=0.024$).

Table 1. Summary descriptive statistics of the patients admitted to the emergency department with an IHI

Parameter	Groups	N	%
Age	2-5	22	29.8
	>5	52	70.2
Gender	Female	20	27
	Male	54	73
Injury mechanism	Traffic accident	16	21.6
	Falling	44	59.4
	Battery	7	9.5
	Foreign body hit on the head	7	9.5
	Total	74	100

For the expressions given with percent to be understood easily, rounding is made after the comma

Table 2. Examination of IHI mechanisms by age groups

Injury mechanism					
	Traffic accident	Falling	Battery	Foreign body hit on the head	total
Groups	n (%)	n (%)	n (%)	n (%)	n (%)
2-5 years	2 (9.1%)	17 (77.3%)	0 (0.0%)	3 (13.6%)	22 (29.8%)
>5 years	14 (26.9%)	27 (51.9%)	7 (13.5%)	4 (7.7%)	52 (70.2%)
		P* = 0.02			74 (100%)

p*=0.02; shows significance according to Fisher's exact test, 2-5 years: represent the toddler age group, >5 years: represent the school-age group. For the expressions given with percent to be understood easily, rounding is made after the comma

Table 3. Types of IHI pathologies and the corresponding numbers and percentages for the localization of injury

Types of Injury Pathologies	n	%
Subarachnoid Hemorrhage	10	13.5
Subdural Hemorrhage	9	12.1
Epidural Hemorrhage	19	25.6
Contusion	14	19
Cranial Bone Fracture	22	29.8
Localization of injury	n	%
Frontal	29	39.1
Parietal	16	21.7
Occipital	12	16.2
Temporal	17	23
Total	74	100

For the expressions given with percent to be understood easily, rounding is made after the comma

In patients exposed to injury, while blood glucose levels were negatively correlated (r=-0.54, p=0.041) with patients in the GCS score of eight and below, it was determined that they were positively correlated with poor prognosis in the emergency department (hospitalization rates) (r=0.44, p=0.045), (Since there were many tables, correlation tables among findings could not be shown).

Discussion

In children, injury is one of the most important health problems of the childhood age group in emergency departments, and it is also the most common cause of mortality. Head injuries are among the most important causes of mortality among all injuries and emerge more dominantly in the male gender (13, 14). Our study findings were compatible with the literature.

When we examine the literature, the rate of head trauma due to "falling" is often higher in the toddler than in the school childhood period (15). Our results are similar to those in the literature, and we predict that it is observed, especially in the toddler period, because children are mobile and do not fully provide balance functions.

Table 4. Indication for surgical treatment according to the Type of Hemorrhage

Indication for surgical treatment	Type of hemorrhage			
	Subdural n	Epidural n	SAH n	Contusion N
S.I.(+)	3	11	0	0
S.I. (-)	6	8	10	14
Total	9	19	10	14

S.I. (+): represents those with surgical indication, S.I. (-): represents those without surgical indications, SAH: subarachnoid hemorrhage

Table 5. Blood WBC, CRP and Glucose parameters according to the GCS subclassification

Blood Parameters	GCS≤8 n = 9	GCS>8 n = 65	P*
WBC (x10³/μL)	18.9 (14.6-22.4)	10.7 (6.8-13.2)	=0.039
CRP (mg/dL)	12.9 (0.2-25.4)	10.8 (0.1-47.9)	=0.34
Glucose (mg/dL)	197.4 (140.9-223)	125.9 (85.6-158)	=0.006

$p^{*}<0.05$; Significance value representing the difference in WBC values according to the GCS subgroups based on the Mann-Whitney U test, $p^{*}<0.01$; Significance value representing the difference in glucose values according to the GCS subgroups based on the Mann-Whitney U test, WBC: leukocyte, CRP: C-reactive protein

Linear fractures are the most common skull pathology in the diagnosis of head injuries and are similar to the literature (8). The reason for the low rate of hemorrhage is considered to be the fact that brain parenchyma is more flexible with regard to hemorrhage in the childhood age group.

According to the CBT results of the patients, when the localizations of pediatric IHI were examined, it was reported that they mostly occurred in the frontal region by 39.1% (Table 3). The fact that the localization of head injuries was found to be high, especially in the frontal region, seems to be compatible with the etiological examinations. In our study, falling cases were the most common cause in the etiology of pediatric head injuries, and it is reported that childhood falls are generally due to falling while running while playing games (16).

In the literature, it is reported that surgical intervention applied in epidural hemorrhages significantly reduces the mortality rates and that these types of hemorrhages are often accompanied by collapse fractures. In this case, the indication for surgical intervention may provide more success (17, 18). In our study, it was investigated whether there was an indication for surgical treatment applied according to the type of hemorrhage. Since there was no death in hospitalized patients, its effect on mortality could not be revealed (Table 4).

When the relationship between the rates of admission to the intensive care unit and the GCS score was examined, while a negative correlation was found between the rate of admission to the intensive care unit and the GCS score ($r=-0.4$, $p<0.05$), the relationship between the GCS score and good prognosis (discharge with full recovery from the emergency department) in the emergency department was significant ($p<0.05$), which was found to be compatible with previous studies (16).

Although the effect of injury on the immunological system has been investigated since the early 1970s, only a few publications have referred to pediatric patients. Epidemiological and clinical data show that children are less susceptible to complications after injury compared to adults (19). The systemic acute-phase response is characterized by leukocytosis. Therefore, although it seems possible that increases in WBC, which are known as white blood cells (leukocytes), and the acute-phase reactant CRP in blood serve as an additional diagnostic and prognostic marker in addition to GCS scoring and CT findings in head injury, this issue has been discussed by many researchers. For example, in the study conducted by Pągowska-Klimek et al. (19), while it was reported that leukocytosis (15.9 x10³/μL) during hospital admission had no significant prognostic value in patients with pediatric head injury with the GCS score of ≤ 9, it was observed that the results of their study were consistent with the results of the study conducted by Chiaretti et al. (20). Furthermore, the researchers suggested that the leukocytosis clinical picture, which was observed suddenly 1 hour after brain injury, was due to sudden increases in the number of granulocytes (19). However, beyond all of them, there are also literature data that are incompatible with these views. In a study conducted by Gürkanlar et al. (21), the predictability of WBC in the severity of head injuries was investigated. While WBC values exceeding 17.5 $x10^6/L$ were found to be effective in predicting the low GCS score and prolonged hospital stay, it was reported that it tended to be observed mainly in patients with moderate and severe head injuries with CT progression. In our study, the relationship between WBC values according to the GCS subgroups of pediatric patients with a head injury was investigated. The WBC median value (18.9 $x10^3/\mu L$) of the group with the GCS subgroup of eight and below was found to be statistically significant and higher compared to the group with the GCS score of above eight (10.7 $x10^3/\mu L$) ($p<0.05$) (Table 5). Furthermore, it was determined that WBC values were negatively correlated ($r=-0.49$, $p<0.05$) with patients with the GCS score of eight and below, and positively correlated with poor prognosis in the emergency department (hospitalization rates) ($r=0.48$, $p<0.05$). A positive correlation between high WBC values and increases in NEU($r=0.8$, $p<0.05$) suggests that the high WBC value in the group with the GCS score of eight and below may be due to increases in NEU dominance.

According to the investigations we conducted, it was observed that there was a limited number of studies in which blood CRP values were investigated in pediatric head injuries other than adults. In a study conducted by Kalabalikis et al. (12), in 45 pediatric patients with traumatic brain injury who were followed up in intensive care for 72 hours, the relationship between the severity of injury and CRP and IL-6 levels was examined. According to the results of the study, while the difference in CRP levels at the 24th and 48th hours between the groups with the GCS score of eight and below and the group with the GCS score of above eight (the group with GCS ≤ 8 24th hour = approximately 80 mg/L; the group with GCS > 8 24th hour = approximately 50 mg/L, and at the 48th hour, CRP levels were higher and at the peak in both groups) was found to be significant, no correlation was found between IL-6 and CRP levels and mortality or neurological outcomes of the patients (12). In a study conducted in Egypt, the researchers reported that CRP levels in pediatric patients were not different between the surviving group and the ex group, and they provided results showing that they had no effect on prognosis (22). In one of the most recent studies conducted by Giden et al. (23) from Turkey, the levels of many biochemical markers in head injuries in pediatric patients were investigated, and they reported that CRP levels were not satisfactory in terms of diagnosis and prognosis of the disease. In our results, the mean CRP levels of our patients at the time of emergency admission after injury were found to be approximately 11.4 mg/dL, and the difference between the medians of the CRP levels (the group with the GCS score ≤ 8; the group with 12.9 mg/dL and GCS > 8; 10.8 mg/dL) according to the subgroups of the GCS score was not found to be statistically significant (Table 5). It is observed that the results of our study confirm other studies mentioned above. According to the results of the present study, although CRP levels appear to be increased more than approximately two times compared to the panic value (<0.5 mg/L), we should keep in mind that it can also be caused by other reasons such as inflammation and infection that increase CRP levels. Furthermore, the fact that the difference between the groups in terms of CRP levels was found to be insignificant suggests that it may be because blood samples of patients were taken within the first 4-6 hours after injury. Although CRP levels are known as an acute-phase protein which can increase and decrease very quickly in response to inflammation and infection, it was shown in the literature that peak levels in the blood could be reached at the 24th or 48th hour of tissue damage, and it was reported that these peak values were associated with poor prognosis (12).

In our study, in addition to the relationship between the blood glucose levels as a result of a head injury at the time of arrival to the hospital and the severity of head injuries observed in pediatric patients, the relationship between glucose levels and inflammation markers was also examined. Our main purpose here was to reveal whether secondary increases in glucose levels due to inflammation, predicted to increase due to injury, and these increases had an effect on the prognosis (hospitalization rates) of our pediatric patients in the emergency department. When the literature data were reviewed, apart from the opinions of 3 authors (24-26) on this subject, most researchers demonstrated that glucose levels had strong prognostic significance in pediatric and adult patients with severe head injuries (27, 28). According to the results of our study, blood glucose median values at the time of admission to the hospital were found to be statistically significant between the subgroups of the GCS score (the group with the GCS score ≤ 8; the group with 197.4 mg/dL and GCS > 8; 125.9 mg/dL) ($p<0.01$) (Table 5). In patients exposed to injury, while blood glucose levels were negatively correlated ($r=-0.54$, $p<0.05$) with patients with the GCS score of eight and below, it was determined that they were positively correlated with poor prognosis in the emergency department (hospitalization rates) ($r=0.44$, $p<0.05$). In line with the literature, the results suggest that blood glucose levels may help predict the severity of injury and may also be a negative prognostic factor in pediatric severe head injuries. Our results also suggest that hyperglycemia observed due to injury in our pediatric patients may develop secondary to increased inflammation because, as a result of injuries occurring in the hypothalamic-pituitary-adrenal axis or various inflammatory events, there are increases in corticotropin-releasing hormone (CRH) levels and accordingly adrenocorticotropic hormone (ACTH) release. Furthermore, we think that nitric oxide (NO) synthesized at the time of inflammation may have caused the release of corticosterone, and consequently, secondary hyperglycemia may have developed or become aggravated. However, we think that more studies are needed to clarify the association between inflammation and hyperglycemia.

In conclusion, it was found that early blood glucose and WBC levels in pediatric severe IHI were effective in revealing the severity of injury and had an effect on the prognosis in the emergency department.

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