



Research Paper

Association Between Serum Electrolyte Disturbances and Glasgow Coma Scale Score in Patients With Diffuse Axonal Injury



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Running Title Serum Electrolytes Levels and GCS Score in Patients with DAI

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ABSTRACT

Background: Appropriate clinical measures to prevent secondary brain damage in traumatic brain injury are of critical importance.

Objectives: This study aims to investigate the relationships between serum electrolyte disturbances and Glasgow Coma Scale (GCS) score in patients with Diffuse Axonal Injury (DAI) at the time of admission and discharge.

Materials & Methods: In this retrospective cross-sectional study, we evaluated 101 patients with DAI having GCS score <15 admitted to Poursina Hospital in Rasht, Iran from 2019 to 2020. Based on the presence or absence of serum potassium (K), sodium (Na), magnesium (Mg), and zinc (Zn), disturbances on the first day of hospitalization, patients were divided into two study groups of with and without abnormal electrolyte levels. The GCS scores of the two groups at the time of admission and discharge were recorded and the relationship between electrolyte disturbances and GCS score was evaluated.

Results: There were no significant differences in the mean GCS score at the time of admission and discharge between patients with and without disturbances in serum Na, K, Zn and Mg levels based on the crude analysis. Regarding the simultaneous effects of the study variables on the GCS score, only Mg serum level exerted a significant impact on the GCS score at the time of admission ($P=0.041$) and discharge ($P=0.017$).

Conclusion: The GCS score in patients with DAI at the time of admission and discharge has an association with the Mg serum level but not with Na, K, and Zn levels.

Keywords: Diffuse axonal injury, Electrolytes, Glasgow Coma Scale

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Highlights

- There was an association between GCS score and Magnesium level in patients with diffuse axonal injury;
- There was no any association between GCS score and sodium, potassium zinc levels in patients with diffuse axonal injury.

Introduction

Traumatic Brain Injury (TBI) is one of the most common causes of mortality in people aged 1-45 years in North America, leading to various disabilities with high socio-economic burden [1]. The overall incidence of TBI in the United States is 538.2 per 100,000 people [1]. The TBI has two types of primary and secondary TBI. Current clinical approaches to manage TBI are based on this classification. Surgical treatment of primary TBI is performed at a primary center for the management of severe cases. On the other hand, diagnosis, prevention, and treatment of secondary TBI are important principles for the management of severe cases [3, 4]. Common mechanisms of primary TBI include direct impact, acceleration/deceleration, penetrating injury, and blast injury. Although these seem to be heterogeneous, they have common feature of exerting external mechanical forces to the brain. The resulting trauma consists of focal cerebral contusions, hematomas, and DAI associated with cerebral edema [5, 6]. Secondary TBI often results from different molecular mechanisms that begin during the primary trauma and continue for hours and days. Some of these mechanisms include glutamate-induced overstimulation, cell membrane damages induced by free radicals, mitochondrial dysfunction, vascular wall injuries, inflammatory responses, apoptosis, ischemia induced by vasospasm, local occlusion of microvasculature, and electrolyte disturbances [7, 8].

Serum electrolyte disturbances in TBI patients are considered as preventable secondary consequences of brain injury and can be resulted from the trauma itself, iatrogenic causes, or other conditions such as renal failure, cirrhosis, and congestive heart failure [9-11]. The risk of electrolyte disturbances in TBI patients depends on the severity of injury, the presence or absence of underlying diseases, age, and initial treatment strategies such as resuscitation fluid selection, mannitol or diuretics administration, and hyperventilation [12]. Disturbances in the serum levels of sodium [9], potassium [14], magnesium [15], and zinc [16] are common, but they are preventable secondary consequences (e.g., cerebral edema, increased intracranial pressure, decreased consciousness

level, and worsening brain damage) in patients suffering from Diffuse Axonal Injury (DAI). The DAI is a type of TBI at the junction of the gray and white matter. Detecting such imbalances in the serum levels of electrolytes could lower the mortality and morbidity rates of primary or secondary TBI [14]. In this study, we aim to investigate the relationship between common serum electrolyte disturbances and the Glasgow Coma Scale (GCS) score in patients with DAI.

Materials and Methods

This is a retrospective cross-sectional study performed on patients with DAI admitted to Poursina Hospital in Rasht, Iran from 2019 to 2020. Patients with a consciousness level below 15 were enrolled in the study. Exclusion criteria were hospitalization for less than three days, being diagnosed with liver or kidney diseases, renal insufficiency, uptake of drugs causing electrolyte disturbances, having serious visceral or orthopedic injuries, having a lesion or hematoma based on CT scan potentially associated with the loss of consciousness, a history of brain surgery or other surgeries.

The lab data of patients were recorded from their medical files during hospitalization. Based on the presence or absence of serum potassium (K), sodium (Na), magnesium (Mg), and zinc (Zn) disturbances on the first day of hospitalization, patients were divided into two study groups of with and without serum electrolyte disturbances. The GCS scores of the two groups were recorded at the time of admission and discharge. The patients were discharged when their serum electrolyte levels were within the normal range.

Descriptive statistics such as frequency, percentage, Mean±SD were used to describe the data. For the assumptions of parametric tests, the normality of data distribution was assessed by Kolmogorov-Smirnov test, and the homogeneity of variances was examined using Levene's test. For normally distributed quantitative variables, independent t-test was used to compare the mean scores between the study groups. In case of abnormal distribution, Mann Whitney U test was used for comparison. To assess the simultaneous effects of

independent variables on the study outcome, linear regression was employed. Fisher's exact test was used to compare the study outcome between the two groups of patients. All statistical analyses were performed in SPSS software v. 26 at a statistically significance level of $P < 0.05$.

Results

The mean age of patients was 34.78 ± 19.64 years, where 88 (87.1%) were males and the rest were females. The mean GCS scores at the time of admission and discharge were 10.10 ± 3.67 and 13.64 ± 2.35 , respectively. Overall, disturbed serum Na, K, Mg, and Zn were detected in 15 (14.9%), 16 (15.8%), 37 (36.6), and 41 (40.6%) patients, respectively.

Based on the results of crude analysis, there were no significant differences in GCS score of patients with and without abnormal levels of Na, K, Zn and Mg neither at the time of admission (Table 1) nor at the discharge time (Table 2).

According to the results in Table 3 regarding the simultaneous effects of study variables on the GCS score at the time of admission, only Mg serum level exerted a

significant impact on the GCS score ($P = 0.041$), where a 1.84-unit decrease in GCS caused an increase per unit in serum Mg level.

According to the results in Table 4 regarding the simultaneous effects of study variables on the GCS score at the time of discharge, only Mg serum level exerted a significant impact on the GCS score ($P = 0.017$), where a 1.42 unit decrease in GCS caused an increase per unit in serum Mg level.

Discussion

Serum Na, K, Mg, and Zn disturbances in patients with DAI are common, but are preventable, secondary complications [12-16]. In our study, we investigated the association between the GCS score and serum electrolyte levels in hospitalized patients with DAI at the time of admission and discharge. The mean GCS score at the time of admission and discharge were 10.10 ± 3.67 and 13.64 ± 2.35 , respectively. Among the participants, 15 (14.9%) presented with disturbed Na, 16 cases (15.8%) with impaired K, 37 (36.6%) with abnormal Mg, and 41 (40.6%) had disturbed Zn levels. There were no significant differences in mean GCS score between patients

Table 1. Comparison of GCS scores at the time of admission between the two groups of patients

Electrolytes	Mean \pm SD/GCS Score		P
	Without Serum Electrolyte Disturbances	With Serum Electrolyte Disturbances	
Na	10.23 \pm 3.75	9.29 \pm 3.14	0.555
K	10.17 \pm 3.71	9.75 \pm 3.59	0.482
Mg	10.72 \pm 3.58	9.38 \pm 3.41	0.133
Zn	10.41 \pm 3.71	9.65 \pm 3.16	0.320

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Table 2. Comparison of GCS scores at the time of discharge between the two groups of patients

Electrolytes	Mean \pm SD/GCS Score		P
	Without Serum Electrolyte Disturbances	With Serum Electrolyte Disturbances	
Na	13.65 \pm 2.48	13.54 \pm 1.39	0.175
K	13.64 \pm 2.40	13.64 \pm 2.09	0.808
Mg	13.88 \pm 2.46	13.21 \pm 2.11	0.182
Zn	13.55 \pm 2.16	13.78 \pm 2.66	0.653

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Table 3. Regression analysis results for assessing simultaneous effects of study variables on the GCS score at the time of admission

Variables	Unstandardized β	Standard Error	Standardized β	T	P
Na	0.01	0.06	0.02	0.20	0.840
K	0.08	0.88	0.01	0.09	0.930
Mg	-1.84	0.89	-0.22	2.07	0.041
Zn	0.02	0.03	0.06	0.53	0.594
Gender	1.61	1.10	0.15	1.45	0.149
Age	0.02	0.02	0.12	1.19	0.237

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with and without disturbances in serum Na, K, Zn and Mg levels at the time of admission and discharge.

One of the interesting topics in recent years has been the impact of sodium disturbance on the prognosis of patients with TBI. We identified no significant relationships between the GCS score and serum Na level at the time of admission in patients with DAI. It was found that 14.9% of patients had Na disturbances. This is against the results of other studies. Paiva et al. revealed a higher incidence of Na disturbance in patients with cerebral hemorrhage, subdural hematoma, DAI, and diffuse cerebral lesions compared to those suffering from brain contusion [17]. For example, Maggiore et al. reported that hyponatremia was associated with a three-fold increase in the risk of mortality in the TBI patients hospitalized in the intensive care unit [18]. Lee et al. recognized severe hyponatremia as an independent risk factor of mortality in the patients admitted to the neurosurgery intensive care unit [19]. Cintra et al. reported a higher incidence of serum Na disturbance in patients who died in the first week after TBI compared to survivors [20]. The discrepancy between our findings and the results of

mentioned studies may be due to the difference in the study population and duration of follow-up period; in our study, DAI patients were adult and all had consciousness levels below 15, while Yousefichaijan et al. assessed 110 patients aged one month to 18 years. So, it seems that Na disturbance in patients with DAI, despite an impact on the prognosis of patients, have no significant effect on short-term GCS scores during hospitalization, suggesting that the associations between hyponatremia and mortality in TBI patients are independent of the GCS score [18-20, 24]. In another study, Yousefichaijan et al., showed a significant relationship between Na disturbances and GCS score in hospitalized patients with TBI [25]. Moreover, some studies such as Buharyet al. in 2017, reported a significant decrease in GCS score associated with an increase in serum Na levels in patients with TBI [11]. This may indicate that over time and during longer hospitalization periods, the relationship between serum Na levels and GCS score may become more clinically and statistically significant. In favor of such theory, a study reported a lower mortality rate in patients who had hyponatremia at the time of admission compared to those hospitalized for several days [26].

Table 4. Regression analysis results for assessing simultaneous effects of study variables on the GCS score at the time of discharge

Variables	Unstandardized β	Standard Error	Standardized β	T	P
Na	0.01	0.04	0.02	0.27	0.784
K	-0.36	0.60	-0.06	-0.59	0.552
Mg	-1.42	0.58	-0.26	-2.43	0.017
Zn	0.008	0.01	-0.04	-0.39	0.695
Gender	0.11	0.71	0.01	0.15	0.878
Age	0.01	0.01	0.14	1.36	0.177

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According to the results of the present study, though 15.8% of patients had serum K disturbances, there were no significant relationship between serum K level and GCS score. In a study by Pin-On et al. in 2018, who investigated the prevalence of water and electrolyte disturbances and their effects on the prognosis and mortality of TBI patients after surgery, hypokalemia was identified as the most common electrolyte disturbance in the patients [27]. It was reported that hypernatremia, hyponatremia, and hypokalemia were the most common electrolyte disturbances in TBI patients with mild (GCS score 13-15) and moderate (GCS score 9-12) conditions before and after surgery. In patients with a severe condition (GCS score <8), however, the most common electrolyte disturbance were hypokalemia followed by hyponatremia [27]. Buhary et al. in 2017, reported a significant relationship between GCS score and serum K levels in TBI patients [11], while we found no significant relationship between the mean GCS score at the time of admission and serum K disturbance. This difference may be due to the fact that in our study, the relationship of serum K level was assessed with the GCS score at the time of admission, while in Buhary et al.'s study, the GCS score was recorded during hospitalization.

Magnesium plays a critical role in improving and repairing secondary brain injuries [15]. Low levels of serum Mg have been reported in patients with diseases such as TBI [28]. For example, Dhandapani et al., reported a significantly lower serum Mg level in patients with severe TBI compared to the controls [29]. Although the mechanism of serum Mg depletion in TBI patients is unknown, increased lipolysis following TBI has been suggested to increase catecholamines and subsequently the serum levels of free fatty acids that bind to Mg and enhance its urinary excretion [30, 31]. Experimental studies have proposed the role of Mg in the activation of N-methyl-D-aspartate receptors and inhibition of glutamate release [32], in the opening of calcium channels [33], as well as lipid peroxidation, free radical production, and apoptosis [34]. The role of Mg in suppressing apoptosis in damaged neurons may be related to its ability to inhibit apoptosis-related proteins such as p53 and Bax in cortical neurons after TBI [35]. According to our results, 36.6% of patients with DAI had serum Mg disturbance. Based on the crude analysis, there was no significant difference in the mean GCS scores between patients with and without serum Mg disturbance, but based on the adjusted analysis, only Mg serum level had significant effect on the GCS Score. Accordingly, each unit of increase in serum Mg predicted a decrease in the GCS score at the time of admission and discharge; however, it was unexpected considering the role of Mg in

improving brain injuries, suggesting a direct correlation between the GCS score and serum Mg level.

In the present study, 40.6% of patients had abnormal serum Zn levels, and there were no significant differences in the mean GCS score between patients with and without serum Zn disturbances at the time of admission and discharge. Recent studies have suggested that although the net cerebral Zn level does not change after TBI, the direction of Zn towards affected brain regions causes a decrease in Zn level in one area and an increase in other area [16]. This is important, given that zinc deficiency increases apoptosis and reduces neuronal repair in TBI models in vitro [16]. Considering the relatively long-term effects of Zn on the brain, it seems that acute and short-term changes in serum Zn level cannot significantly affect the GCS score in patients with DAI.

Conclusion

The GCS score in patients with DAI at the time of admission and discharge is related to their serum level of magnesium. Their GCS score has no relationship with serum levels of other electrolytes including sodium, potassium zinc.

Ethical Considerations

Compliance with ethical guidelines

All study procedures were in compliance with the ethical guidelines of the 2013 Declaration of Helsinki. This study was approved by the ethics committee of [Guilan University of Medical Sciences](#) (Code: IR.GUMS.REC.1398.329).

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Authors' contributions

Conceptualization and Methodology: Hamid Behzadnia, Shahrokh Yousefzadeh-Chabok., Mohammadreza Emamhadi, Mesbah Dibavand; Investigation, Writing Original Draft, Review & Editing: All authors; Resources and Supervision: Hamid Behzadnia, Mesbah Dibavand.

Conflict of interest

The authors declared no potential conflicts of interest.

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