

Effect of Early Correction of Hyponatremia on Neurological Outcome in Traumatic Brain Injury Patients

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Abstract

Background: Hyponatremia is common in neurocritical care. If it is timely corrected, it can prevent deadly complication like brain edema and may improve overall prognosis in these patients.

Methods: Retrospective analysis of 150 patients of traumatic brain injuries who developed hyponatremia during stay in intensive care unit (ICU) was performed. Neurological outcome was defined on the basis of Glasgow Coma Scale (GCS), comparing GCS on admission and GCS at the time of discharge from ICU. Good neurological outcome was defined, if GCS improved significantly as compared to admission and poor neurological outcome if GCS remained same or deteriorated than admission or patient died during ICU stay. On the basis of correction of serum sodium within 48 h of onset of hyponatremia, two groups (correction achieved or not) were compared to the neurological outcome groups, as defined earlier. Chi Square test and Multiple Logistic Regression Model were used to assess association between correction of hyponatremia within 48 h & neurological outcome. Data was analyzed by SPSS Version 21 and Stata Statistical Package 13. P value < 0.05 was considered significant.

Results: Majority of patients were male, 88% versus 12% of females. Mean age remained 32.7 years. In 108 patients correction of hyponatremia was achieved within 48 h and in 42 cases it took longer time to correct. Good neurological outcome was seen in 83% cases and poor outcome in 17%. Statistically significant association was seen between serum sodium correction within 48 h of onset and neurological outcome (Chi Square, P < 0.0001), (Logistic Regression analysis, P < 0.001 in univariate & 0.007 in multivariate analysis).

Conclusion: There is significant association between early correction of hyponatremia and neurological outcome in traumatic brain injury patients.

Keywords: Traumatic brain injury; Hyponatremia; Intensive care unit; Neurological outcome; Glasgow coma scale; Brain edema; Acute hyponatremia

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Introduction

Hyponatremia is the most common electrolyte abnormality seen in critically ill patients [1]. Patients with polytrauma and traumatic brain injury are the most critically ill patients, and hyponatremia is frequently seen in these patients [2-4]. Hyponatremia is one of the common causes of secondary brain injury [5]. If it is not corrected promptly, it may cause serious complications such as

malignant brain edema leading to brainstem herniation, and eventually to death [6]. In this way hyponatremia can affect the

overall neurological outcome and hospital morbidity & mortality [7-10]. Hyponatremia is defined as if serum sodium level falls below 135 mmol/L [11]. If hyponatremia duration is less than 48 h it is called acute hyponatremia [12] and chronic if more than 48 h of onset [13]. Soon after hypotonic environment due to hyponatremia, compensatory mechanisms start working by extruding intracellular minerals (sodium & chloride) and organic osmolytes to extracellular space to maintain water equilibrium between brain cells. It is the acute hyponatremia in which the chances of cerebral edema are more as compared to chronic one, as these compensatory mechanisms are not fully developed yet [14,15]. Thus, if serum sodium is not corrected during this time, the chances of complications like cerebral edema due to water shift into the brain cells are more which may lead to serious consequences [16]. In this way sodium correction during this duration (within first 48 h of onset) may directly correlate to the neurological outcome and can affect the overall prognosis [17].

All the traumatic brain injury (TBI) patients are classified into three severity classifications, according to the initial Glasgow Coma Scale (GCS); mild TBI (GCS 13-15), moderate TBI (GCS 9-12) and severe TBI (GCS 3-8) [18,19].

There are many studies done in the past to find out various factors affecting on neurological outcome, but to see early correction of hyponatremia affecting neurological outcome in traumatic brain injury patients, are scarce. Thus, this study was designed to determine the influence of the early hyponatremia's correction on neurological outcome in these patients.

Methodology

Methods

A retrospective analysis of 150 patients who were admitted to surgical, medical & neurosurgical intensive care units (ICU) diagnosed with different traumatic brain injuries and developed hyponatremia during their ICU stay, was performed in a tertiary care hospital level one trauma center. All those patients who remained in a persistent shock state (MAP < 65 mm Hg & persistent rising lactate), persistent hypoxia due to any reason (with persistent $PO_2 < 60$ mm Hg & $SaO_2 < 90\%$), having concomitantly any metabolic encephalopathy, and fixed-dilated pupils with initial GCS 3/15 due to initial neurological insult, were excluded from the study. Two groups were defined on the basis of serum sodium (s.Na) correction (≥ 135 mmol/l) within 48 h of detection, whether correction achieved or not. Hyponatremia was defined as serum sodium level < 135 mmol/L. A lowest value of three readings < 135 mmol/L was recorded in each case, each reading 4 h apart. Neurological outcome was defined on the basis of comparing their GCS on admission to hospital (prior to endotracheal intubation) and at the time of discharge from ICU. Good neurological outcome was defined if GCS improved significantly than admission, i.e., in severe TBI if GCS improved ≥ 11 , in moderate TBI if GCS improved by ≥ 2 scores, in mild TBI if GCS improved by ≥ 1 score as compared to admission. In Severe TBI GCS is between 3-8, in moderate TBI between 9-12 and in mild TBI between 13-15. Both groups, neurological outcome

group (Good/Poor) and sodium correction with 48 h (achieved or not), were compared to know statistical association between these two variables.

Study design

It was an observational descriptive analysis.

Data Collection & Statistical Analysis

Data was collected by using Philip IntelliVue Portfolio-Clinical Information System, being used in our set up for documentation of patient clinical record. Categorical variables were described as frequencies or percentages, and continuous variables as mean & standard deviation (SD). Categorical variables (neurological outcome & Na correction within 48 h) were compared using Chi Square test and continuous variables (mean serum Na levels before & after treatment) by Paired Student T Test. Multivariable Logistic Regression Model was used to know the association between neurological outcome and other factors including sodium correction with 48 hours. Data was analyzed by SPSS Version 21 for basic calculations as well Chi Square Test, and Stata Statistical Package 13 for Logistic Regression Model. An alpha value of 5% (P value < 0.05) and confidence interval of 95% was considered as significant statistically.

Results

The mean age remained 32.73 ± 18.24 SD years. Most common age groups remained 25-36 years 31% (47/150) & 37 to 48 years 21% (32/150). Nine per cent (13/150) belonged to above 60 years age group. Male patients were 132 (88%) and eighteen (12%) females. Seven patients (5%) died amongst study population, and 143 (95%) were discharged from the ICU after stabilizing and treating the initial injuries. Mean value of total length of stay (LOS) in ICU remained 16.16 ± 9.8 SD days (minimum of 2 days & maximum 55 days). The highest mean LOS was seen in severe TBI cases, 18.3 ± 8.9 SD days. Road traffic accident (RTA) and fall from height remained the two most common causes of TBI, 46% (70/150) & 41% (61/150), respectively. Other causes leading to initial TBI were, due to industrial accidents in 9% (13/150), Sports injury in 2% (3/150), 2 patients (1.3%) due to assault and 1 case (0.6%) due to gun-shot injury (**Figure 1**). Sixty per cent (90/150) patients were classified as severe TBI on the basis of initial GCS score, 19% (29/150) with moderate TBI and 21% (31/150) with mild TBI (**Figure 2**). In 67% (100/150) patients, mixed lesions with combination of two or more different TBI categories were noted. While solitary lesions were noted in 31% (47/150) cases, such as extradural hematoma, contusion hematoma, traumatic subarachnoid hemorrhage & traumatic intraventricular hemorrhage. Diffuse Axonal Injury (DAI) was diagnosed in 2% (3/150) cases on the basis of clinical & Magnetic Resonant Imaging (MRI) findings (**Figure 3**). The most common mode of GCS on admission was found 8 (23 patients out of 150, 15%). The most common mode of GCS at the time of discharge from ICU remained 15 (64 patients out of 150, 43%). Amongst the 90 cases with severe TBI, 38 (42%) patients had initial GCS 3-5 & 52 (58%) patients with GCS between 6-8. In 54% (81/150) patients different neurosurgical procedures were performed like decompressive

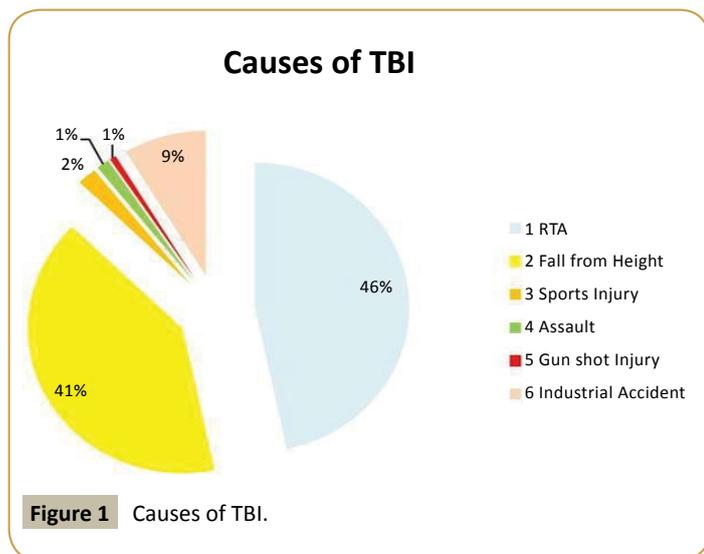


Figure 1 Causes of TBI.

Severity	n
Mild (GCS 13-15)	31
Moderate (GCS 9-12)	29
Severe (GCS 3-8)	90
TOTAL	150

Figure 2 TBI severity.

craniectomy, craniotomy with evacuation of hematoma, external ventricular drainage and intracranial pressure monitoring (ICP) as isolated or in combination with other procedures. While in 46% (69/150) cases, only medical management was provided or neurosurgical intervention was not required. The mean serum sodium level before correction was 131.20 ± 2.91 SD mmol/L and mean serum sodium level after treatment of hyponatremia was 137.58 ± 2.45 SD mmol/L (Table 1). Severe hyponatremia (serum sodium <125 mmol/L) was seen only in 3% (4/150) cases, with lowest value of 117 mmol/L. The mean duration of onset of hyponatremia remained 7.74 ± 7.00 SD days after ICU admission. Serum sodium was corrected to normal in 72% (108/150) patients within 48 h of onset of hyponatremia, while in 28% (42/150) cases it took longer than 48 h to be corrected due to delayed or wrong diagnosis of hyponatremia. In 98% (147/150) patients this correction was achieved by <12 mmol/L/24 h, while in 3 cases (2%) exceeded >12 mmol/L/24 h. The neurological outcome as defined earlier in methods, good outcome was seen in 83% (125/150) patients and poor outcome in 17% (25/150) cases, from all types of TBI (mild, moderate & severe). While

in 90 patients with severe TBI, good neurological outcome was observed in 76% (68/90) patients & poor neurological outcome in 24% (22/90) patients (Table 1). Statistical significant association was seen between serum sodium correction within 48 h of onset (Yes/No) and neurological outcome group (Good/Poor), Chi Square Test ($X^2: 19.285; Df=1; P \text{ value} < 0.0001$) (Table 2). This

Table 1 Demographic data and basic information. Total number of patients (n): 150.

Age	(Mean) 32.7 ± 18.24 SD Years	
Gender		
➤ Mae	132 (88%)	
➤ Female	18 (12%)	
Patient Status		
➤ Discharged from ICU	143 (95%)	
➤ Died during ICU Stay	7 (5%)	
Length of Stay in ICU	(Mean) 16.16 ± 9.8 SD Days	
Average GCS		
➤ On admission	8	
➤ At discharge from ICU	12	
TBI Classification		
➤ Mild	31 (21%)	
➤ Moderate	29 (19%)	
➤ Severe	90 (60%)	
TBI Lesions		
➤ Mixed	100 (67%)	
➤ Solitary	47 (31%)	
➤ DAI	3 (2%)	
Onset of Hyponatremia	(Mean) 7.7 ± 7 SD Days	
Mean Serum Sodium		
➤ Before treatment	131.20 ± 2.91 SD Mmol/L	
➤ After treatment	137.58 ± 2.45 SD Mmol/L	
Serum Sodium Correction in 48 h		
➤ Yes	108 (72%)	
➤ No	42 (28%)	
Neurological Outcome		
• In all TBI (mild, moderate, severe)	Good 125/150 (83%)	Poor 25/150 (17%)
• In Severe TBI n: 90	68/90 (76%)	22/90 (24%)

TBI Categories	n
Mixed Lesions	100
Solitary Lesions (n:47)	
EDH	10
SDH	16
CH	14
tr SAH	5
IVH	2
DAI	3
TOTAL	150

Figure 3 TBI categories.

Table 2 Association between serum sodium correction within 48 h and neurological outcome.

Neurological Outcome	Serum Sodium Correction within 48 h		Total
	Yes	No	
Good	99/150 (66%)	26/150 (17%)	125/150 (83%)
Poor	9/150 (6%)	16/150 (11%)	25/150 (17%)
Total	108/150 (72%)	42/150 (28%)	150/150 (100%)

Chi Square Test (2 × 2 Table) X²: 19.285, Df: 1, P value<0.0001

Table 3 Association between neurological outcome and other factors including sodium correction within 48 h of detection.

Variables	Odds Ratio	Z-Statistic	P-Value	Lower limit 95% CI	Upper limit 95% CI
Na correction within 48 h	10	2.7	0.007	1.9	55
Age	0.98	-1.18	0.24	0.94	1.02
Female Gender	2.11	0.57	0.57	0.16	27
GCS on admission	0.51	-2.86	0.003	0.33	0.8
GCS on discharge	3.43	4.22	<0.001	1.93	6.08

Univariate analysis: Odds Ratio (OR) of good neurological outcome if Na correction done within 48 h=5.44 (P value<0.001, 95% - 2.2-13.48)

Multivariable logistic regression model to assess neurological outcome

association was seen also statistically significant by Univariate and Multivariable Logistic Regression Model (Univariate analysis: odd ratio (OR) of good neurological outcome if Na correction within 48 h=5.44, P value<0.001, CI 95% -2.2-13.48), (Multivariable Logistic Regression Model to assess neurological outcome, OR for Na correction within 48 h=10, P value 0.007 CI 95% 1.9-55). Same way, significant association was seen between neurological outcome and GCS at admission (OR 0.51, P value 0.003, CI 95% 0.33-0.8) & GCS at discharge (OR 3.43, P value<0.001, CI 95% 1.93-6.08). However, there was no statistical significance between neurological outcome and age (OR 0.98, P value 0.24, CI 95% 0.94-1.02) & gender (OR 2.11, P value 0.57, CI 95% 0.16-27) (**Table 3**). Receiver operator characteristic Curve for Logistic Model, area under ROC Curve was 0.9731 (**Figure 4**).

Discussion

Hyponatremia is very common in traumatic brain injury patients, and it is one of significant risk factor leading to secondary brain injuries [5]. The risk of complications like cerebral edema is more within first 48 h of onset due to water shift into brain cells because of low osmolality as compared to chronic hyponatremia (onset >48 h), as most of compensatory mechanisms are not fully developed in acute hyponatremia [11-15]. Thus, if hyponatremia is corrected appropriately within this duration, serious complication like malignant brain edema can be prevented. Our study was designed to know the effect of hyponatremia correction within first 48 h of onset on neurological outcome in traumatic brain injury patients, who were admitted to ICU. In our study, we found road traffic accident (RTA) most common cause leading to TBI and majority of these patients were young male. In 108 patients serum sodium was normalized within 48 h of

detection of hyponatremia and in 42 patients, it took more than 48 h to correct. In 125 cases, good neurological outcome was observed and poor outcome in 25 patients. We found a significant association between early correction of hyponatremia within 48 h of detection and neurological outcome in these patients. I could not find any exactly similar study in the literature to compare my results, but our study resembled with some recently published studies with common objectives but different variables.

Xiao et al. [20] conducted recently a retrospective analysis on 136 patients with traumatic brain injuries, and he found correlation between developing hyponatremia and factors such as GCS ≤ 8, cerebral oedema, and a basal skull fracture. In his study, by multivariate logistic regression analysis he found a strong association between occurrence of hyponatremia and a GCS ≤ 8 (P<0.016), presence of cerebral edema (P<0.001), and a basal skull fracture (P<0.001), but no statistical significant association between occurrence of hyponatremia and age (P>0.05) and gender (P=0.347). In our study, there were 90 cases with GCS ≤ 8 who had developed hyponatremia during ICU stay. We found a significant association between correction of hyponatremia within 48 h and neurological outcome based upon GCS scoring (OR 5.44, P Value<0.001, CI 95% - 2.2-13.48), but no statistically significant association between neurological outcome and age & gender (P value 0.29 & 0.58, respectively). These results are little comparable to his study, anyhow he measured only epidemiology of hyponatremia and we measured association between neurological outcome and sodium correction within 48 h of onset.

Georg et al. [21] conducted a large multicenter retrospective analysis on 77 ICUs (medical, surgical & mixed ICUs) on 151486 patients and determined that dysnatremia is independent risk factor for increased mortality in critically ill patients. He included all the patients at the time of ICU admission who had hyponatremia or hypernatremia. He found that all grades of hyponatremia (mild, moderate & severe) were associated with increased risk of mortality, OR and 95% confidence interval for borderline, mild & severe hyponatremia were 1.32 (1.25-1.39), 1.89 (1.71-2.09) and 1.81 (1.56-2.10), respectively. We had single center study and only traumatic brain injury patients with hyponatremia were analyzed,

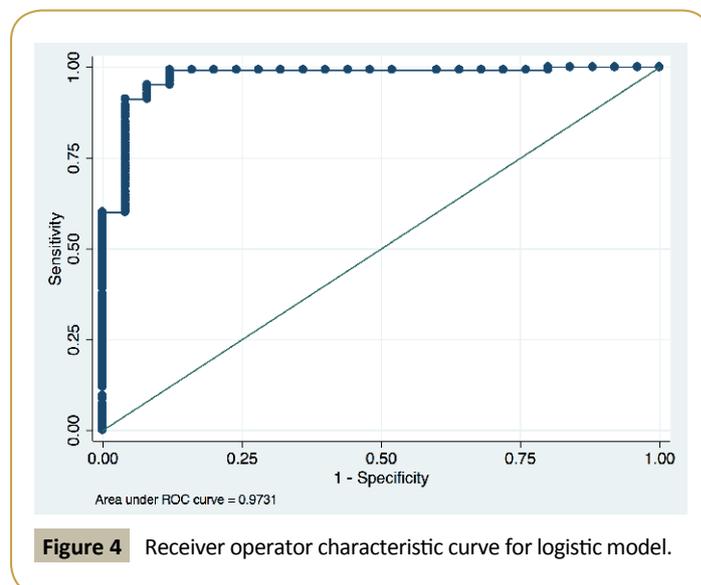


Figure 4 Receiver operator characteristic curve for logistic model.

in contrast to his multicenter and all population of ICU patients who had dysnatremia. He included all dysnatremic patients on admission to ICU, while we had analysis on only TBI patients who developed hyponatremia during ICU stay after admission. He had 1.2% of cases with severe hyponatremia, while we had 3% (4/150) cases with severe hyponatremia. Overall ICU mortality in his study was 12%, while it was only 2% (3/147) in ours. Mean age was 62 ± 16 in his study population, while it was 32.73 years in our study. The average LOS was 16 days in our study, while it was 4 days in his study. The main strength of our study remained that we measured neurological outcome on the basis of serum sodium correction within acute phase (<48 h of onset), when the chances of severe cerebral edema are more due to shift of water into brain cells because of hypo-osmolality. While, he measured only the consequences of dysnatremia. He did not measure the effect of any intervention on overall outcome in these patients.

Gopinath et al. [22] conducted a prospective study and measured effect of arterial hypoxia as a cause of secondary brain injury on neurological outcome in patients with severe traumatic brain injury (GCS ≤ 8). He used fiber optic catheter to detect jugular venous desaturation (SjvO₂) in 116 patients admitted with severe head injuries and found significant association between SjvO₂ and poor neurological outcome. His study was comparable to ours in few aspects, 90 per cent of patients studied were male, with average age of 31.5 ± 14.7 years. We had 60% cases with severe TBI, while he had all patients included in the study with severe TBI. Mean age was 32.7 years in our, which remained quite similar to his study, explaining again the higher incidence of traumatic brain injury in young population. However, he used Glasgow Outcome Scale (GOS) to measure neurological outcome, while we used Glasgow Coma Scale (GCS) to measure neurological outcome as long term functional outcome like GOS was not possible in our study due to rapid turn-over of patients from ICU to general ward after stabilizing and treating the initial insults. Moreover, he had prospective study, while we had retrospective analysis in our study and further studies may be required in a prospective fashion.

Dias et al. [23] investigated response of hypertonic saline bolus on intracranial hypertension in traumatic brain injury patients, and he found significant reduction of intracranial pressure after intravenous bolus of hypertonic saline. Devin et al. [24] conducted a study on animal model by using osmotic transport device (OTD) in patients with traumatic brain injury who had severe cerebral oedema and he found significantly improved functional neurological outcome in OTD treated patients. Both these studies above indicate that any factor causing reduction in cerebral oedema in acute traumatic brain injury patients, can improve neurological outcome. Our study was based upon the similar concept of correcting hyponatremia in acute phase (within 48 h of onset) when there is increased risk of cerebral oedema, which if treated appropriately can improve the neurological outcome.

Limitations of Study

We had some limitations in our study. Firstly, it was retrospective analysis, while many studies done in past are prospective while determining outcome. It was a single center study, further multicenter studies on a large sample size may be required further to validate this concept. We used Glasgow Coma Scale as a tool for outcome, while in many studies done in past to measure the neurological outcome, Glasgow Outcome Scale had been used as a tool for neurological outcome.

Conclusion

Hyponatremia is one of the important factors affecting neurological outcome. Timely and effective correction of hyponatremia may improve outcome in patients with traumatic brain injury. Its early correction within acute phase (within 48 h of onset), when there is increased risk of cerebral oedema, can improve neurological outcome significantly.

Authors Contribution

1. **Khalil Ahmad:** Main conception & design of study, manuscript drafting.
2. **Zeyad Faour Alrais:** Critical revision of manuscript.
3. **Hesham Mohamed Elkholy:** Acquisition of data.
4. **Adel Elsaid Elkholy:** Draft revision.
5. **Maged Mohsen Beniamein:** Acquisition & Interpretation of data.
6. **Ammar Mohamed Abdelhadi:** Acquisition & Interpretation of data.
7. **Sohail Majeed:** Participated in Study Protocol & data interpretation.
8. **Ahmad Shoab:** Data Analysis.

Ethical Approval

Prior approval was taken from local ethical committee, Medical Research Committee, Dubai Health Authority. Ref: MRC-05/2014-10.

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