

A Prospective Study on Hyponatremia in Traumatic Brain Injury

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Abstract

Background Hyponatremia is the commonest electrolyte imbalance in traumatic brain injury (TBI) with a reported incidence of 15 to 20%.

Methodology A prospective observational analytical study was conducted from January 2015 to December 2015. Mild and moderate TBI patients aged between 13 and 65 years, with no comorbid conditions were included in the study. Patients were monitored for hyponatremia, and etiology was found out using standard investigation protocol.

Results A total of 153 patients were included in the study. Incidence of hyponatremia was 21.6% (33/153). Cerebral salt wasting syndrome was more common than syndrome of inappropriate secretion of antidiuretic hormone. Incidence was higher in patients with low Glasgow coma scale score ($p = 0.001$) and in patients with parenchymal contusions ($p = 0.008$). Incidence correlated well with Marshal computed tomography (CT) score ($p = 0.013$). No significant difference of incidence was noted in relation to age or gender. Patients with hyponatremia had significantly prolonged intensive care unit ($p < 0.001$) and hospital stay ($p < 0.001$). Outcome at discharge was worse in patients with hyponatremia ($p = 0.002$), whereas both groups had similar outcome at 3-month follow-up ($p = 0.087$).

Conclusions Hyponatremia is a very common electrolyte imbalance in patients of TBI. Marshal CT grading and initial Glasgow coma scale score correlate well with the incidence of hyponatremia. More aggressive sodium monitoring may be required in parenchymal contusions in view of increased chance of development of hyponatremia. Hyponatremia adversely affect the immediate outcome in TBI, while long term outcome is usually unaffected.

Keywords

- ▶ hyponatremia
- ▶ head injury
- ▶ cerebral salt wasting

Introduction

Hyponatremia is a common electrolyte abnormality in a hospital setting and is defined as serum sodium level less than 135 meq/L.^{1–3} Hyponatremia is a common electrolyte imbalance among patients of traumatic brain injury (TBI), with incidence varying from 15 to 30%.^{4–6}

Hyponatremia is an excess of water in relation to the sodium in the extracellular fluid. It is important to recognize hyponatremia because of the potential morbidity and mortality. Identifying the etiology and risk factors for the development of hyponatremia will help in better anticipation of hyponatremia in hospitalized patients and minimize the complications associated with hyponatremia. Hyponatremia is

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often misdiagnosed and unnecessary treatment is given. So it is better to diagnose the hyponatremia in the early stage itself so that severe hyponatremia does not occur in patients. Moreover, it is to be remembered that rapid correction of severe hyponatremia can lead to central pontine myelinolysis which is a dreaded complication.⁷ So anticipating a disorder that can be treated with simple measures when detected properly is of great importance for the doctor and patient.

Aims and Objectives

This study aims to measure the incidence of hyponatremia in patients with TBI admitted in a tertiary care hospital. We also aim to find out if there is any difference in incidence of hyponatremia with the type of injury and whether the incidence of hyponatremia adversely affects the outcome of the patients with TBI.

Methodology

This was a hospital based prospective observational study. All patients with mild and moderate TBI (Glasgow coma scale [GCS]: 8–15) admitted to Aster MIMS Calicut from January 1, 2015, to December 31, 2015, aged 13 to 65 years, were included in the study. All patients with previously diagnosed medical and surgical conditions which produce hyponatremia were excluded. SPSS 17.0 software (IBM) was used for statistical analysis. Chi-square test for comparing proportion was used for finding the significance.

Patients were interviewed on the basis of a set of questions pertaining to their previous medical history and investigations to exclude those patients with previous medical histories that may produce hyponatremia.

Patients with TBI were graded on the basis of Marshall computed tomography (CT) grading. Hyponatremia was divided into mild, moderate and severe based on the sodium values in the serum.

- (i) Mild hyponatremia 131 to 134 meq/L
- (ii) Moderate hyponatremia 120 to 130 meq/L
- (iii) Severe hyponatremia <120 meq/L

The diagnostic approach to the patient with hyponatremia consists of a directed history and physical examination, appropriate laboratory tests, and in selected patients, assessing the response to volume expansion with isotonic saline.

Although medical history and physical examination often provide important clues to the cause of hyponatremia, identification of subtle degrees of volume depletion or edema may be difficult. Hence patients with past history of hypothyroidism or previous surgical history of total thyroidectomy or physical findings suggestive of an underlying disease were excluded from this study. Three laboratory tests along with the physical examination findings in all patients were used to decide the etiology of hyponatremia:

- (a) Serum osmolality
- (b) Urine specific gravity

(c) Urine sodium concentration

Serum osmolality was calculated on the basis of the following formula:

$$\text{Serum osmolality} = 2[\text{Na}^+ + \text{K}^+] + \text{RBS}/18 + \text{BUN}/2.8 \text{ mOsm/L,}$$

where RBS is random blood sugar (mg/dL) and BUN is blood urea nitrogen (mg/dL).

Central venous pressure is taken as the direct parameter reflecting extracellular fluid volume in this study and the criteria for hypovolemia, euvolemia and hypervolemia were taken as follows

- Hypovolemia: 0 to 3 cm of water
- Euvolemia: 4 to 12 cm of water
- Hypervolemia: 13 to 20 cm of water

Of these, we excluded those patients with previous medical causes of hyponatremia from our study by means of history and previous laboratory investigations. In rest of the patients (previously apparently normal patients), we classified the etiology of hyponatremia on the basis of the algorithm given below (►Fig. 1).

Regarding the outcome of patients with hyponatremia, patients with TBI with hyponatremia were followed up and mortality and morbidity rates were compared with those TBI patients without hyponatremia and proportions so obtained are compared using chi-square testing for the significance. Outcome is measured on the basis of the following parameters:

- (a) duration of hospital stay
- (b) duration of intensive care unit (ICU) stay
- (c) Glasgow outcome score at discharge
- (d) Glasgow outcome score at 3 months
- (e) need for readmission

Outcome records were obtained from outpatient/inpatient follow-up records of computerized medical records in MIMS Calicut. For those patients in whom, the hospital records are unavailable, the outcome was assessed on the basis of interview through phone/e-mail.

Results

Demographics

A total of 344 patients were admitted to our hospital during this period with TBI. Of these, after applying the inclusion criteria and exclusion criteria, 153 patients were included in this study. Our study population included the patients with age between 13 and 65 years with a mean age of 32.8 years with standard deviation of 13 years. Thirty-eight patients included in this study were females and accounted for 24.8% of the total sample whereas males accounted for the rest 75.2% (115 out of 153).

Incidence of hyponatremia in our study group was 21.6% (33 patients out of 153). In the patients with hyponatremia, 13 patients (8.5%) had mild hyponatremia (defined by Serum sodium level: 131–134 mEq/L), 13 patients (8.5%) had moderate hyponatremia (defined by serum sodium

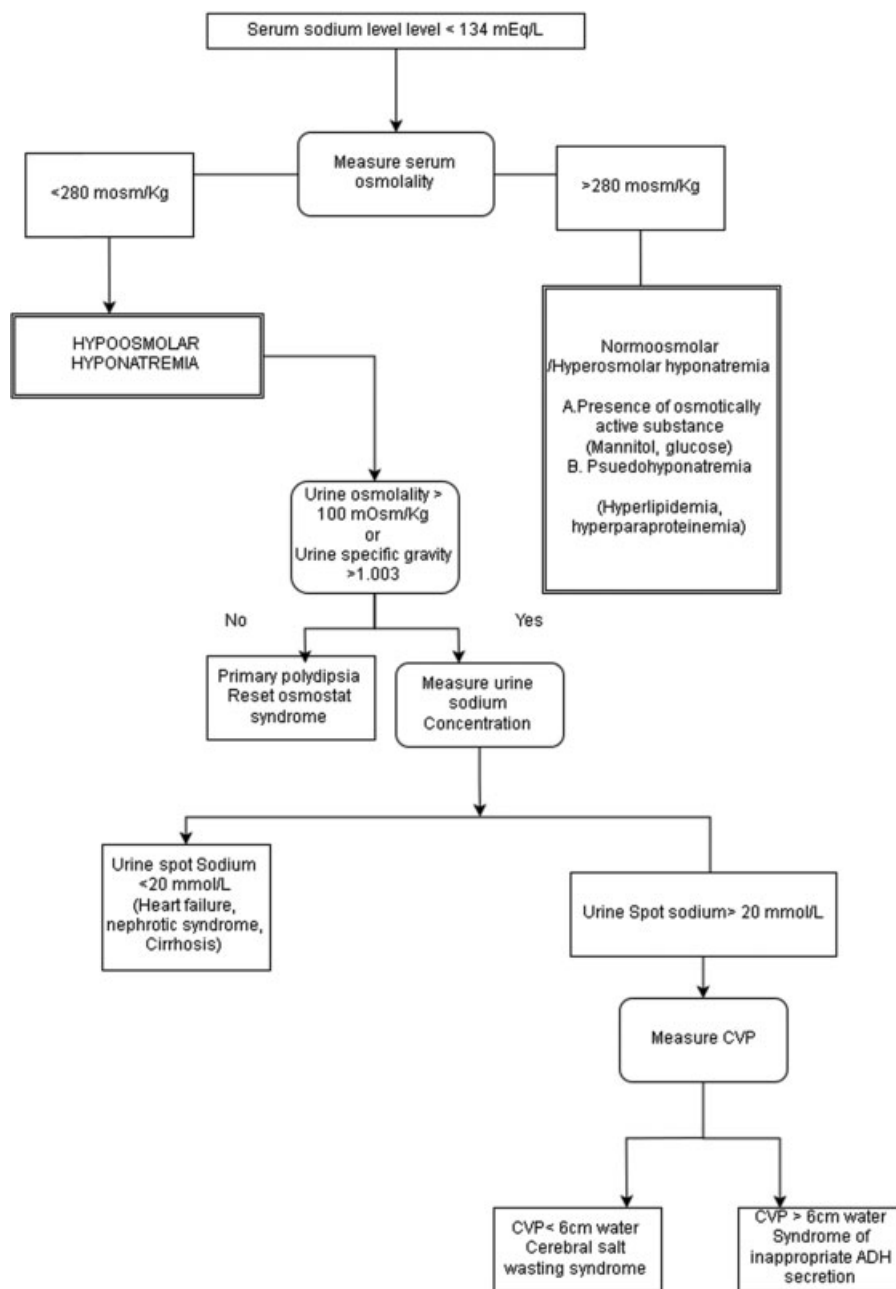


Fig. 1 Algorithm for diagnosing etiology of hyponatremia.

level: 120-130 mEq/L), and 7 patients (4.6%) had severe hyponatremia (► **Table 1**).

Interval between the development of hyponatremia and occurrence of TBI varied between 1 and 55 days with mean of 5 days (standard deviation = 9.89 days) and median of 3 days. Most of the cases of hyponatremia occurred within 1 week of the occurrence of the insult.

Associated injuries occurred in 58 individuals (37.9% of the total study population). Nine patients (5.8%) had more than one system involvement. Maxillofacial injuries accounted for nearly 13% of the injuries involved followed by orthopaedic injuries (12.4%), and ophthalmological

injuries (3%). Chest and spinal injuries accounted for 2.61 and 1.3%, respectively.

Association between Age and Gender with Incidence of Hyponatremia

We analyzed our data to find out if there was any significant difference in hyponatremia based on the age and sex of the patient. We had greater incidence of hyponatremia with increasing age and in females (compared with males), but it was not statistically significant based on further analysis ($p = 0.35$ for age, 0.437 for gender)

Table 1 Epidemiological findings of the study population

	N	Hyponatremia	p
Total no. of patients included in the study	153	33 (21.6%)	
Male	115 (75.2%)	24 (20.9)	0.437
Female	38 (24.8%)	9 (23.7)	
Mean age(years)	32.8 ± 13		0.35
Less than 40 years	106	21 (21.8)	
More than 40 years	47	12 (25.5)	
Hyponatremia			
Mild (131–134 mEq/L)	13 (8.5%)		
Moderate (120–133 mEq/L)	13 (8.5%)		
Severe (<120 mEq/L)	7 (4.6%)		
Severity of injury			
Mild	107	14(13.08)	0.001
Moderate	46	19(41.30)	

GCS and Hyponatremia

We found that in our study group, incidence of hyponatremia was higher in the low GCS groups than with high GCS groups. We had included only patients with GCS > 8 in this study (Severe head injury was excluded). Our analysis showed that the incidence of hyponatremia was lower in the patients with higher GCS. Most of our patients (75) had an initial GCS of 15

of which only 9 patients developed hyponatremia, whereas we had 12 patients with an initial GCS of 9, of which 6 developed hyponatremia. When analyzed between moderate and mild head injury for incidence of hyponatremia, it was found that patients with moderate head injury had higher incidence of hyponatremia (41 vs. 13%). This difference was found to be significant after Fisher exact test with a *p* value of 0.001 (→ **Table 1**).

Marshall CT Grading and Hyponatremia

Most of our patients had a Marshall CT grade of 3 (45%), followed by 2 (30.7%) and 1 (13.7%). We had one patient with grade 5 (0.7%) and no patients with Grade 6. Pearson chi-square test was done in the groups with no hyponatremia and hyponatremia to know the statistical significance of incidence of hyponatremia in relation to the Marshall CT grade. In hyponatremic group, 21 patients had grade 3 (30.3%); 4 patients (26.6%) had grade 4, 5 patients (10.6%) had grade 2, 1 patient had (100%) had grade 5; 2 patients (9.5%) had grade 1. This difference was found to be statistically significant on chi-square testing (*p* = 0.013) (→ **Table 2**).

Type of Brain Injury and Incidence of Hyponatremia

Patients were regrouped on the basis of the type of head injury: EDH, SDH, SAH, Contusion, intracerebral hematoma, intraventricular hemorrhage, and no abnormality detected group. Incidence of hyponatremia was compared in each group with the rest of the patients. There was no statistically significant difference in incidence of hyponatremia in patients with or without EDH, SDH, SAH, and intraventricular hemorrhage and no abnormality detected group. However, relationship between parenchymal contusion and incidence of

Table 2 Radiological findings

	Hyponatremia n (%)	No hyponatremia	p
Marshall CT score			
I: No visible intracranial pathology	2 (9.5)	19	0.013
II: Cisterns present with 0–5 mm of shift)	5 (10.6)	42	
III: Cisterns compressed or absent with 0–5mm of shift	21 (30.43)	48	
IV: Midline shift > 5 mm but no lesion >25 cm ³	4 (26.66)	11	
V: Any lesion surgically evacuated	1 (100)	0	
VI: Any high or mixed density mass lesion > 25 cm ³ not surgically evacuated	0	0	
Intracranial hemorrhage			
Epidural hematoma	9 (27.3%)	24	0.069
Subdural hematoma	11 (33.3%)	22	0.083
Subarachnoid hemorrhage	11 (33.3%)	22	0.083
Contusion	18 (54.5%)	15	0.005
DAI	3 (20%)	12	0.087
NAD	3 (9.3%)	29	0.23

Abbreviations: CT, computed tomography; DAI, diffuse axonal injury; NAD, no abnormality detected.

hyponatremia was found to be statistically significant with a p value of 0.005. This clearly indicates that the patients with parenchymal contusion are more vulnerable to the development of hyponatremia (► **Table 2**). Hence, it is recommended to have aggressive sodium monitoring in the patients with traumatic cerebral contusions

Site of Brain Injury and Hyponatremia

The analysis of our data showed that right and left side of the brain was affected almost equally by the TBI. Further analysis showed that most of our patients had multiple site involved. However, injury seemed to be more in the frontal lobe, followed by temporal lobe, and parietal lobe and occipital lobes were the least affected. However, no statistically significant difference in the incidence of hyponatremia was found with different sites of injury.

Etiology of Hyponatremia

Based on the etiology of hyponatremia, we had 11 patients (33.4% of patients within hyponatremia group, 7.19% of the total study population) diagnosed with Cerebral Salt Wasting Syndrome. We had 2 patients diagnosed with SIADH which accounted for (6.06% of patients within hyponatremia group, 1.3% of the total study population). Diuretic induced hyponatremia (Mannitol) was noted in significant number of individuals (13 patients out of 33, 39.39% of patients within hyponatremia group, 8.49% of the total study population). Hyperosmolar/normo-osmolar hyponatremia (other than diuretic induced) occurred in 6 patients (18.18% of patients within hyponatremia group, 3.92% of the total study population).

Outcome after TBI: Role of Hyponatremia

Mortality

Our analysis showed that hyponatremia affected the outcome in TBI. One patient with moderate head injury on initially recorded GCS had diffuse axonal injury died. He had SIADH. No mortality was recorded in the group of patients

with no hyponatremia. This suggests the probable role of hyponatremia in increasing the mortality rates in TBI.

Morbidity

In our study, morbidity of the patient was recorded by Glasgow outcome score outcome score of the patient. GOS was assessed at the time of discharge and after 3 months of discharge. Most of our patients (68%) had Glasgow outcome score of 4 at the time of discharge. However on 3 months follow up 84.5% of our patients showed to have a GOS of 5. Glasgow outcome score at discharge and after 3 months. Paired T -Test was done to find out role of hyponatremia in determining GOS of the patient. Based on our analysis we found that hyponatremic group had a lower GOS at the time of discharge compared with non hyponatremic group, which was statistically significant ($p = 0.002$). However GOS at 3 months of discharge did not show any significant difference ($p = 0.087$; ► **Table 3**)

Hyponatremia and Prolonged Hospital/ICU Stay

In our study, we found that patients with hyponatremia experienced a longer hospital stay compared with those without hyponatremia. One of our patients had expired and hence she was excluded from calculating ICU stay and inpatient stay period. Mean ICU stay for patients who had hyponatremia was 1.87 compared with patients without hyponatremia who had a mean ICU stay of 0.83 days. Mean hospital stay was 7.34 and 3.93 days respectively for patients with hyponatremia and without hyponatremia. Both these differences were statistically significant with p value < 0.001 (► **Table 3**)

We found that the need for readmission was definitely higher in the hyponatremia group compared with non hyponatremia group. Out of 17 patients who required readmission, 8 patients had hyponatremia in their first admission. After Pearson Chi-Square testing, p value was found to be significant ($p = 0.010$). Patients with recurrence of hyponatremia showed symptoms of headache, vomiting, dizziness and altered sensorium Hence, based on this we suggest the patients with TBI with hyponatremia in their

Table 3 Outcome measures

	Group	Mean	Standard deviation	p
GOS At Discharge	Hyponatremia	3.82	0.683	0.002
	No Hyponatremia	4.18	0.56	
GOS At 3 Months	Hyponatremia	4.58	0.867	0.087
	No Hyponatremia	4.85	0.423	
Mean ICU Stay	Hyponatremia	1.87	1.80	<0.001
	No Hyponatremia	1.05	0.83	
Mean Hospital Stay	Hyponatremia	7.34	4.05	<0.001
	No Hyponatremia	3.93	2.66	

Abbreviations: GOS, Glasgow outcome score; ICU, intensive care unit.
Note: Bold values are statistically significant.

first admission presenting with nonspecific symptoms like headache, dizziness, vomiting should be undergo serum sodium estimation in their outpatient follow up. However, further studies in this regard are required for devising a definitive guideline in this regard.

Discussion

Incidence of hyponatremia in our study was 21.6%. In a study conducted by Moro et al incidence was found to be 16.8%⁸ Similarly, Lohani and Devkota in their study has found the incidence to be 27.2%⁴. Mean age of incidence of hyponatremia was found to be 32.8 years. Median age was 29 years, which was due to the increased occurrence of road traffic accidents (RTAs) among young drivers in their second and third decade of life. Further analysis showed a definitive male predominance in the RTAs, which shows that men are more involved in RTA. In previous similar studies also male gender predominance in RTA was noted^{9,10} However, there was no significant difference in incidence of hyponatremia depending on the sex. Average age was more in hyponatremic group; however, this difference is not statistically significant ($p = 0.35$). Similar conclusions were made by Baozhong et al in their retrospective study.³

In our study, most of our patients developed hyponatremia within 1 week of occurrence of trauma with a mean of 5 days and median of 3 days. This finding correlates well with the previous studies till date. Lohani and Devkota has reported the mean duration to be 1.78 days. However, the study included only 40 TBI patients and probably no late hyponatremia patients were included in the study.⁴

The incidence of hyponatremia was found to be higher in the patients with lower GCS. This difference was statistically significant with a p value of 0.001. Moro et al have described the correlation of initial GCS with hyponatremia⁸. However, this finding is contradictory to the findings of Lohani and Devkota, who reported that initial GCS does not have any predictive value in the incidence of hyponatremia. Doczi et al in their study has reported that hyponatremia occurred more in patients with moderate head injury than in patients with severe head injury.¹¹

Lohani and Devkota have reported the predictive role of Rotterdam CT grading in the incidence of hyponatremia in TBI.⁴ In this study, we used Marshall CT grading and compared the incidence of hyponatremia in each Marshall CT grades. We have found out there is increased incidence of hyponatremia with increase in the Marshall CT grading. This difference was statistically significant with a p value of 0.013. Hence, on the basis of our study, we found that Marshall CT grading has a predictive role in incidence of hyponatremia.

Paiva et al have described the incidence of hyponatremia varies with the type of brain injury and found out that there was greater incidence of sodium disorders in patients with subdural, intracerebral hematoma and with diffuse axonal injury, but this difference was not found to be statistically significant.¹² Our study also showed an increased incidence of hyponatremia in cerebral contusions and diffuse axonal

injuries compared with other type of brain injuries. The difference in the incidence was found to be statistically significant in case of cerebral contusion. These findings did not seem to match with the findings of Paiva et al,¹² who suggested that patients with diffuse lesions have a higher chance of developing hyponatremia.

Lohani and Devkota have reported that frontal lesions to be more common in TBI, and hence hyponatremia, was more common in frontal lesions⁴ In our study, we had more patients with frontal lobe involved, followed by temporal and parietal lobes, and occipital lobe and brainstem were least affected. Incidence of hyponatremia was found to be similar in the different sites of brain lesions, and no statistically significant differences could be made out.

Most of our patients had hyponatremia due to diuretic induced hyponatremia. Patients with hypoosmolar hyponatremia had mostly cerebral salt wasting syndrome (CSWS). This is in accordance with the findings of many authors such as Sorkhi et al who described that there is increased incidence of CSWS in acute neurological disorders in children.¹³⁻¹⁵ However in this study, all acute neurological disorders were included and the study included only the pediatric age group. Similar study conducted by Sherlock et al in 457 patients showed that SIADH to be the important cause of hyponatremia.¹⁶ But the study also included all patients with acute neurosurgical disorders including TBI and cerebral tumors. The study included only 44 patients with TBI and hypothesized that a large percentage of the patients with hyponatremia was due to SIADH, which was drug induced. Many authors, such as Singh et al, have suggested the difficulty in the diagnosis between CSWS and SIADH and suggested that SIADH existed more than that of CSWS.^{5,17-19} In this study, we included only the patients with TBI and found that diuretic induced hyponatremia was more common than CSWS and SIADH. We also found that the incidence of CSWS is higher than that of SIADH

Arief et al have described the role of hyponatremia in increasing the mortality in TBI.²⁰ In our study, we had one mortality in a patient with hyponatremia having diffuse axonal injury. The patient had no associated chest, spinal, orthopedic or OMFS injury, which suggests that secondary insult due to hyponatremia, had a major contribution toward mortality. However, this contradicts with the study conducted by Sherlock et al in SAH patients, where they found out that hyponatremia was associated with prolonged hospital stay, but was not associated with increased mortality.¹⁶

Lohani and Devkota reported that the incidence of hyponatremia did not affect the duration of hospital stay and did not have any significant effect in the Glasgow outcome score of the patient.⁴ However in our study, there is a significant increase in the duration of hospital stay and ICU stay in the patients with hyponatremia compared with non hyponatremic group. Glasgow outcome score of the patients at the time of discharge significantly varied between hyponatremic and non hyponatremic individuals. However, after 3 months of follow-up, there was no significant difference noted in the Glasgow outcome score. In a similar

study with SAH, after 3 months of discharge, Alimohamadi et al have described that incidence of hyponatremia did not affect the outcome of patients.²¹ In our study, we also compared the readmission rates of patients with TBI. We found that readmission rates were more in the hyponatremia group.

Conclusions

Hyponatremia is a very common electrolyte imbalance in TBIs. In most patients, hyponatremia occurred within 1 week of TBI. Marshall CT grading of TBI correlates well with the incidence of hyponatremia. The higher the grade, more are the chances of incidence of hyponatremia. Patients with lower GCS had more chance of developing hyponatremia. Patients with parenchymal contusions and diffuse axonal injuries had higher chances of developing hyponatremia than patients with other types of brain injury. Aggressive serum sodium monitoring may be recommended in these set of patients with traumatic brain injury. Further studies are to be conducted in this regard before getting into final conclusion.

Incidence of CSWS was found to be higher than SIADH. It is necessary to devise further clear cut guidelines for the differentiating both. Incidence of hyponatremia in TBI affected adversely the outcome in traumatic brain injury. Patients with hyponatremia had prolonged hospital and ICU stay as well as decreased GOS at the time of discharge. However, the effect of hyponatremia was not found to be significant on 3-month follow-up. Recurrence of hyponatremia following TBI is not uncommon. Most of the patients present with vague symptoms such as headache, nausea, and positional vertigo. So it is recommended to have higher index of suspicion during outpatient follow up in patients with brain injury and hyponatremia in initial admission. Further studies are required regarding the contributory role of mild hyponatremia in this regard.

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