

Serum Electrolyte Disturbances and their Association with Glasgow Coma Scale Severity in Adults with Traumatic Brain Injury: A Prospective Observational Study from a Tertiary Care Intensive Care Unit in Assam, India

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Abstract

Background: Electrolyte disturbances are common after traumatic brain injury (TBI) and can add to secondary brain damage. We measured serum sodium, potassium, calcium and magnesium during the first week of intensive care and related them to Glasgow Coma Scale (GCS) severity.

Methods: This prospective observational study enrolled 60 consecutive adults with TBI admitted within two weeks of injury to the intensive care unit of Assam Medical College and Hospital, Dibrugarh, from July 2019 to June 2020. Electrolytes and GCS were recorded daily for seven days. Day 1 and day 7 means were compared by t-test, and electrolyte status was related to GCS category by Fisher's exact test.

Results: Mean age was 41.32 ± 13.55 years; 95.0% were men, 85.0% were injured in road traffic accidents and 61.7% had subdural haemorrhage. Over the week, hypernatraemia occurred in 33.3%, hypokalaemia in 23.3%, hypocalcaemia in 20.0%, hyponatraemia in 18.3%, hyperkalaemia in 15.0% and hypomagnesaemia in 13.3% of patients. Mean GCS rose from 7.58 ± 2.66 to 10.42 ± 2.51 ($p < 0.0001$) and abnormal values became less frequent. On day 1, sodium ($p = 0.006$) and potassium ($p = 0.027$) status were associated with GCS, while calcium and magnesium were not. On day 7 all four were associated with GCS ($p = 0.024, 0.011, 0.007$ and 0.010 , respectively), with abnormalities concentrated in patients who remained severely injured.

Conclusion: Sodium and potassium disturbances are common after TBI and cluster in severe injury. Daily monitoring of all four cations through the first week of intensive care is advisable.

Keywords: Traumatic Brain Injury; Glasgow Coma Scale; Hyponatremia; Hypokalemia; Hypocalcemia; Magnesium; Intensive Care Units.

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Introduction

Traumatic brain injury (TBI) is the most common acute neurological disorder seen in hospitals and a leading cause of death and long-term disability among young adults. Dewan and colleagues estimated that about 69 million people (95% CI 64 to 74 million) sustain a TBI each year, and that low- and middle-income countries carry close to three times as many cases, in proportion to population, as high-income countries [1]. The causes also differ by region. In high-income countries most TBI now follows falls in older people, many of whom have other illnesses, while in low- and middle-income countries road traffic

incidents involving motorcyclists and pedestrians remain the main cause [2]. The 2022 Lancet Neurology Commission described TBI as having the highest incidence of all common neurological disorders and drew attention to its long-term consequences, which include an increased risk of late neurodegeneration [2]. India follows the second of these patterns. A review from the National Institute of Mental Health and Neuro Sciences estimated that 1.5 to 2 million people are injured and about 1 million die every year in India, with road traffic injuries causing about 60% of TBIs, falls 20% to 25% and violence about 10%;

alcohol was involved at the time of injury in 15% to 20% of cases [3]. In a population survey in Hyderabad, the adjusted annual incidence of non-fatal road traffic injury was 20.7%, the highest rates were among pedestrians, riders of motorised two-wheelers and cyclists, and road traffic mortality was 38.2 per 100,000 population per year [4]. Most of those injured are of working age. A death or a permanent disability in this group removes an earner from the household and places a long burden of care on the family. Some patients also reach a tertiary centre only after fluids and drugs have been started at a peripheral hospital, which makes the first laboratory values harder to interpret.

Brain damage after trauma develops in two phases. The primary injury occurs at the moment of impact and includes contusion, laceration, diffuse axonal injury and intracranial haemorrhage. Secondary injury evolves over the following hours and days through ischaemia, failure of energy-dependent ion pumps, calcium overload, excitotoxicity, oxidative stress, inflammation and cerebral oedema [2].

Systemic insults such as hypotension, hypoxia, fever and disordered fluid and electrolyte balance make this cascade worse. Intensive care cannot reverse the primary injury, so most of its effort goes into limiting secondary damage. Severity is graded at the bedside with the Glasgow Coma Scale (GCS), which adds eye, verbal and motor responses into a score of 3 to 15 [5]. Scores of 13 to 15, 9 to 12 and 3 to 8 are usually taken to indicate mild, moderate and severe injury, and the score is repeated through the stay to follow recovery or deterioration.

The brain also controls the body's handling of water and salt. Osmoreceptors in the anterior hypothalamus sense plasma osmolality and regulate the release of antidiuretic hormone (ADH) from the posterior pituitary, and the hypothalamic-pituitary axis governs adrenal, thyroid and other endocrine function. Trauma to the hypothalamus, the pituitary stalk or the gland itself can therefore upset fluid and electrolyte balance. In a systematic review of 19 studies with 1,137 patients, Schneider and colleagues found a pooled prevalence of hypopituitarism of 27.5% in the chronic phase after TBI, with a higher prevalence after severe than after mild or moderate injury [6]. Disorders of the posterior pituitary appear early. Among 102 survivors of moderate or severe TBI, Agha and colleagues found that 21.6% had developed diabetes insipidus (DI) and 12.9% the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in the immediate post-injury period; DI was more frequent after severe injury, and 6.9% still had DI when tested a median of 17 months later [7].

Sodium is the main determinant of plasma osmolality, and because the intact blood-brain barrier is relatively impermeable to sodium, a change in serum sodium moves water into or out of brain tissue. A fall in sodium favours cerebral oedema and a rise in intracranial pressure, while a rapid rise draws water out of brain cells. Hyponatraemia after TBI may result from SIADH, from cerebral salt wasting, or simply from excess hypotonic fluid. Hypernatraemia may result from central DI, from osmotherapy with mannitol or hypertonic saline, from fever and insensible loss, or from inadequate free water in patients who cannot drink [8]. Plasma osmolality is normally 280 to 300 mOsm/kg and is set almost entirely by sodium and its accompanying anions. Glucose and urea contribute only a few per cent, and urea crosses cell membranes freely, so it exerts little effective osmotic pressure. In most capillary beds plasma proteins hold fluid within the vessel, but cerebral capillaries are joined by tight junctions that also hold back small ions, so total osmolality rather than oncotic pressure governs water movement across them [8]. This is why osmotic agents reduce brain water, and why a fall in sodium is poorly tolerated after brain injury. The mechanism matters for treatment: SIADH is managed by restricting water, whereas cerebral salt wasting needs salt and volume replacement, and treating one as the other can harm the patient [8].

Both directions of sodium change have been linked to worse outcomes. In a retrospective series of 298 patients with TBI, Moro and colleagues found hyponatraemia in 16.8%; it was associated with a longer hospital stay ($p < 0.001$) and an unfavourable outcome ($p = 0.02$), and 13 of the 50 hyponatraemic patients had marked natriuresis that needed hydrocortisone in addition to sodium supplements [9]. Among 130 mechanically ventilated patients with severe TBI, Maggiore and colleagues detected hypernatraemia in 51.5%, mostly mild with a mean of 150 mmol/L, and after adjustment for baseline risk its occurrence during the stay carried a hazard ratio for death of 3.00 (95% CI 1.34 to 6.51) [10]. In 881 patients in a neurosurgical intensive care unit (ICU), Li and colleagues reported mortality of 20.6%, 42.4% and 86.8% with mild, moderate and severe hypernatraemia, against 2.0% in patients whose sodium stayed below 150 mmol/L [11].

Potassium changes are just as frequent, though they have been studied less. Pomeranz and colleagues found an average serum potassium of 3.1 ± 0.4 mmol/L on arrival in 46 patients with severe isolated head trauma (GCS 7 or less); the hypokalaemia appeared within hours of injury and resolved with treatment during the first day [12]. They attributed it to the catecholamine surge that accompanies severe head injury, which drives

potassium into cells through beta-2 adrenergic stimulation of the sodium-potassium pump [12]. Osmotic diuresis with mannitol, beta-agonist nebulisation and hyperventilation can lower serum potassium further in the ICU. In a cohort of 375 hypokalaemic patients with TBI, Wu and colleagues found that severe hypokalaemia peaked between 24 and 96 hours after injury, and that a lower GCS (OR 1.27) and a lower potassium level (OR 4.35) were each independently associated with death [13].

Calcium and magnesium are involved in the secondary injury itself. A large and sustained influx of calcium into neurons activates proteases and endonucleases and starts cell death pathways, and the route by which calcium enters the cell appears to matter as much as the absolute intracellular level [14]. Movement of calcium into injured tissue, transfusion of citrated blood and changes in plasma proteins can all lower the measured serum calcium. Magnesium is a cofactor for the sodium-potassium ATPase and a physiological blocker of the N-methyl-D-aspartate receptor channel, so a low magnesium level may favour excitotoxic calcium entry. In 31 men with brain injury, Cernak and colleagues found that plasma magnesium and calcium fell immediately after injury in those with a GCS of 4 to 6 and stayed low for the full seven days of observation, whereas in mild injury magnesium was low only until day 3. Magnesium balance correlated negatively with markers of oxidative stress [15]. Low magnesium also tends to travel with low potassium and low calcium, because magnesium depletion impairs renal potassium conservation and the release of parathyroid hormone, so these disturbances often appear together in the same patient. Most of the studies cited above measured sodium alone or recorded several electrolytes only at admission. Fewer have followed sodium, potassium, calcium and magnesium together through the first week of intensive care and related each day's values to the GCS recorded on the same day. Such data would show which disturbances are most frequent, when they occur and whether they track the depth of injury, which in turn helps an ICU decide how often to test and which abnormalities to anticipate. We hypothesised that electrolyte disturbance is common after TBI and is more frequent in patients with a lower GCS. The present study was carried out to estimate serum sodium, potassium, calcium and magnesium daily during the first seven days of ICU stay in adults with TBI, and to examine the association of these values with GCS severity on day 1 and day 7.

Aims and Objectives

The aim of the study was to estimate serum electrolyte levels in adult patients with traumatic brain injury admitted to the intensive care unit.

The specific objectives were (1) to measure serum sodium, potassium, calcium and magnesium daily from day 1 to day 7 of ICU admission and determine the frequency and type of electrolyte disturbance; (2) to compare electrolyte levels and GCS on day 1 with those on day 7; and (3) to examine the association between electrolyte status and GCS severity on day 1 and on day 7.

Materials and Methods

Study Design and Setting: This was a prospective, hospital-based observational study carried out in the intensive care unit of the Department of Anaesthesiology and Critical Care, Assam Medical College and Hospital, Dibrugarh, Assam, a tertiary referral centre for Upper Assam. The study ran for one year, from July 2019 to June 2020.

Ethical Approval and Consent: The Institutional Ethics Committee (Human) of Assam Medical College approved the protocol before recruitment began. Because most patients could not give consent themselves, the study procedure was explained to each patient's legal guardian in a language they understood, and written informed consent was obtained from the guardian. Participation did not alter the treatment that patients received.

Participants: Adults aged 18 years or older of either sex who were admitted to the ICU with TBI within two weeks of injury were eligible. Patients were excluded if the guardian refused consent; if there was another likely cause of electrolyte disturbance; if the brain insult had another cause such as hypertension, cerebrovascular disease or infection; if the patient was pregnant; if there was a history of end-organ dysfunction or chronic diuretic therapy; if the head injury was more than two weeks old; if the TBI was accompanied by major trauma to the heart, lungs, kidneys or other organs; if there was a known endocrine disorder; or if the patient died within seven days of admission.

Sample Size and Sampling: All patients who met the inclusion and exclusion criteria during the study year were enrolled consecutively, so no formal sample size calculation was made. Sixty patients were included and all completed the seven-day observation period.

Data Collection: Age, sex, mode of injury and the diagnosis made on non-contrast computed tomography (NECT) of the brain were recorded on a pretested proforma at admission.

Venous blood was drawn every day from day 1 to day 7 of admission, and serum sodium, potassium, calcium and magnesium were measured in the Department of Biochemistry. The GCS was assessed and recorded every day over the same

period. Intravenous fluids and osmotic agents given to each patient were noted.

Laboratory Methods and Reference Ranges:

Sodium and potassium were measured by direct ion-selective electrode, calcium by the colorimetric arsenazo III method and magnesium by a colorimetric formazan dye method. The laboratory reference ranges were 136 to 145 mEq/L for sodium, 3.5 to 5.1 mEq/L for potassium, 8.6 to 10.2 mg/dL for total calcium and 1.6 to 2.6 mg/dL for magnesium. Values above or below these ranges were classified as hyper- or hypo-states of the respective electrolyte (for example hypernatraemia or hyponatraemia).

Assessment of Severity: Injury severity was classified each day from the GCS [5] as mild (13 to 15), moderate (9 to 12) or severe (3 to 8).

Clinical Management: All patients were managed according to the institutional TBI protocol, which included airway and ventilatory support as needed, intravenous fluids, osmotherapy for raised intracranial pressure, antibiotics and other supportive drugs. Electrolyte abnormalities detected on daily testing were corrected according to the same protocol, with treatment individualised by the treating team.

Outcome Definitions: For the overall frequency of each disturbance, a patient was counted as abnormal if any value during the seven days fell outside the reference range, and was assigned to the hyper- or hypo- category that was recorded. Day-wise frequencies were based on that day's value. Day 1 values were compared with day 7 values,

and electrolyte status on day 1 and day 7 was cross-tabulated against GCS category on the same day.

Statistical Analysis: Data were entered in a master chart and analysed with SPSS for Windows, version 16.0. Categorical variables are presented as numbers and percentages and continuous variables as mean $\pm$ standard deviation (SD). Mean electrolyte values and GCS on day 1 and day 7 were compared with Student's t-test. The association between electrolyte status (hyper, hypo or normal) and GCS category (mild, moderate or severe) was tested with the Fisher-Freeman-Halton extension of Fisher's exact test, because many cells in the 3×3 tables had expected counts below five. A two-sided p value below 0.05 was taken as statistically significant.

Results

Sixty patients were enrolled and all completed the seven-day observation period. Their baseline characteristics are shown in Table 1. Ages ranged from 18 to 75 years, with a mean of 41.32 ± 13.55 years and a median of 41.5 years; the largest group was aged 41 to 50 years (28.3%). Fifty-seven patients (95.0%) were men. Road traffic accidents caused 85.0% of injuries and falls the remaining 15.0%.

On NECT, subdural haemorrhage was the commonest lesion (61.7%), followed by subarachnoid haemorrhage (20.0%), extradural haemorrhage (8.3%), diffuse axonal injury (6.7%) and intracerebral haemorrhage (3.3%). All patients received normal saline; one-third also received half-normal saline and one-third mannitol, and 18.3% received 3% hypertonic saline.

Table 1: Baseline characteristics of the study patients (n = 60)

Characteristic	N	%
Age group (years)		
18-20	5	8.3
21-30	10	16.7
31-40	14	23.3
41-50	17	28.3
51-60	9	15.0
61-70	4	6.7
71-80	1	1.7
Mean $\pm$ SD (years)	41.32 ± 13.55	
Median (range) (years)	41.5 (18-75)	
Sex		
Male	57	95.0
Female	3	5.0
Mode of injury		
Road traffic accident	51	85.0
Fall	9	15.0
Diagnosis on NECT brain		
Subdural haemorrhage	37	61.7
Subarachnoid haemorrhage	12	20.0
Extradural haemorrhage	5	8.3
Diffuse axonal injury	4	6.7

Intracerebral haemorrhage	2	3.3
Intravenous fluids and osmotic agents*		
Normal saline (0.9%)	60	100.0
Half-normal saline (0.45%)	20	33.3
Mannitol	20	33.3
Hypertonic saline (3%)	11	18.3

NECT: non-contrast computed tomography; SD: standard deviation. *Categories are not mutually exclusive.

Frequency of electrolyte disturbance: Table 2 gives the number of patients with at least one abnormal value during the first seven days. Sodium was the electrolyte most often deranged, in 31 patients (51.7%); 20 (33.3%) had hypernatraemia and 11 (18.3%) hyponatraemia. Potassium was abnormal in 23 patients (38.3%), with hypokalaemia in 14 (23.3%) and hyperkalaemia in 9 (15.0%). Calcium was abnormal in 17 patients

(28.3%), with hypocalcaemia in 12 (20.0%) and hypercalcaemia in 5 (8.3%).

Magnesium was the most stable, abnormal in 10 patients (16.7%), of whom 8 (13.3%) had hypomagnesaemia and 2 (3.3%) hypermagnesaemia. Hypernatraemia was the single commonest disturbance, followed by hypokalaemia and hypocalcaemia.

Table 2: Patients with at least one abnormal electrolyte value during days 1 to 7 (n = 60)

Electrolyte	Raised, n (%)	Low, n (%)	Normal throughout, n (%)	Any abnormality, n (%)
Sodium	20 (33.3)	11 (18.3)	29 (48.3)	31 (51.7)
Potassium	9 (15.0)	14 (23.3)	37 (61.7)	23 (38.3)
Calcium	5 (8.3)	12 (20.0)	43 (71.7)	17 (28.3)
Magnesium	2 (3.3)	8 (13.3)	50 (83.3)	10 (16.7)

Raised: hypernatraemia (>145 mEq/L), hyperkalaemia (>5.1 mEq/L), hypercalcaemia (>10.2 mg/dL), hypermagnesaemia (>2.6 mg/dL). Low: hyponatraemia (<136 mEq/L), hypokalaemia (<3.5 mEq/L), hypocalcaemia (<8.6 mg/dL), hypomagnesaemia (<1.6 mg/dL).

Day-wise course: The daily frequencies of each disturbance are shown in Tables 3 and 4, and Figure 1 plots them against the proportion of patients with severe injury. Hypernatraemia was present in 16 patients (26.7%) on day 1, stayed between 23.3% and 26.7% until day 5 and then fell to 7 patients (11.7%) by day 7. Hyponatraemia fell from 9 patients (15.0%) on day 1 to 2 (3.3%) on day 7. Hypokalaemia fell from 11 patients (18.3%) to 3 (5.0%) and hyperkalaemia from 8 (13.3%) to 2 (3.3%), with the steepest fall after day 4. The decline in abnormal potassium after day 4, and in abnormal sodium after day 5, coincided with the

fall in the proportion of patients with severe injury (Figure 1).

Hypocalcaemia declined from 11 patients (18.3%) to 4 (6.7%) and hypercalcaemia from 4 (6.7%) to 2 (3.3%). Hypomagnesaemia affected 6 or 7 patients (10.0% to 11.7%) each day until day 5 and 3 patients (5.0%) on days 6 and 7, while hypermagnesaemia never involved more than 2 patients on any day. By day 7 the proportion of patients with normal values had risen to 85.0% for sodium, 91.7% for potassium, 90.0% for calcium and 93.3% for magnesium.

Table 3: Day-wise distribution of serum sodium and potassium status (n = 60)

Day	Sodium raised	Sodium low	Sodium normal	Potassium raised	Potassium low	Potassium normal
Day 1	16 (26.7)	9 (15.0)	35 (58.3)	8 (13.3)	11 (18.3)	41 (68.3)
Day 2	15 (25.0)	6 (10.0)	39 (65.0)	7 (11.7)	9 (15.0)	44 (73.3)
Day 3	15 (25.0)	7 (11.7)	38 (63.3)	8 (13.3)	11 (18.3)	41 (68.3)
Day 4	16 (26.7)	6 (10.0)	38 (63.3)	7 (11.7)	10 (16.7)	43 (71.7)
Day 5	14 (23.3)	7 (11.7)	39 (65.0)	3 (5.0)	8 (13.3)	49 (81.7)
Day 6	10 (16.7)	4 (6.7)	46 (76.7)	1 (1.7)	4 (6.7)	55 (91.7)
Day 7	7 (11.7)	2 (3.3)	51 (85.0)	2 (3.3)	3 (5.0)	55 (91.7)

Values are n (%). Raised = hypernatraemia or hyperkalaemia; low = hyponatraemia or hypokalaemia.

Table 4: Day-wise distribution of serum calcium and magnesium status (n = 60)

Day	Calcium raised	Calcium low	Calcium normal	Magnesium raised	Magnesium low	Magnesium normal
Day 1	4 (6.7)	11 (18.3)	45 (75.0)	1 (1.7)	6 (10.0)	53 (88.3)
Day 2	4 (6.7)	10 (16.7)	46 (76.7)	1 (1.7)	6 (10.0)	53 (88.3)
Day 3	4 (6.7)	11 (18.3)	45 (75.0)	2 (3.3)	6 (10.0)	52 (86.7)
Day 4	3 (5.0)	7 (11.7)	50 (83.3)	2 (3.3)	7 (11.7)	51 (85.0)
Day 5	5 (8.3)	8 (13.3)	47 (78.3)	2 (3.3)	7 (11.7)	51 (85.0)
Day 6	3 (5.0)	4 (6.7)	53 (88.3)	1 (1.7)	3 (5.0)	56 (93.3)
Day 7	2 (3.3)	4 (6.7)	54 (90.0)	1 (1.7)	3 (5.0)	56 (93.3)

Values are n (%). Raised = hypercalcaemia or hypermagnesaemia; low = hypocalcaemia or hypomagnesaemia.

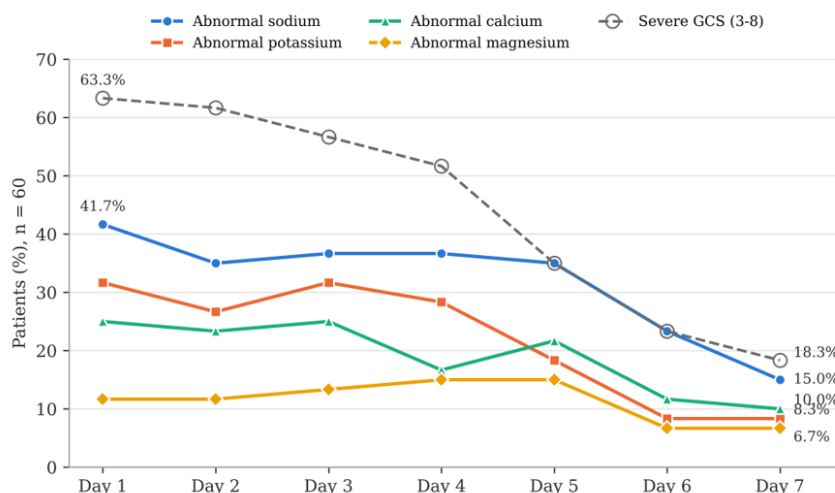


Figure 1: Proportion of patients (n = 60) with an abnormal serum sodium, potassium, calcium or magnesium value on each day of the first week, shown with the proportion in the severe GCS category (3 to 8). Abnormal includes both raised and low values. Data from Tables 3 to 5. On days 5 and 6 the sodium and severe-GCS proportions coincide (35.0% and 23.3%)

Glasgow Coma Scale: On day 1, 38 patients (63.3%) had severe injury, 18 (30.0%) moderate and 4 (6.7%) mild injury (Table 5). The severe group shrank gradually, most clearly between days 4 and 6, and on day 7 11 patients (18.3%) remained in the severe category, 37 (61.7%) were moderate

and 12 (20.0%) mild. Many patients who moved out of the severe category gained only one or two points and crossed into the moderate range.

Mean GCS rose from 7.58 ± 2.66 on day 1 to 10.42 ± 2.51 on day 7 ($p < 0.0001$; Table 6).

Table 5: Day-wise distribution of injury severity by Glasgow Coma Scale (n = 60)

Day	Mild (GCS 13-15), n (%)	Moderate (GCS 9-12), n (%)	Severe (GCS 3-8), n (%)
Day 1	4 (6.7)	18 (30.0)	38 (63.3)
Day 2	5 (8.3)	18 (30.0)	37 (61.7)
Day 3	4 (6.7)	22 (36.7)	34 (56.7)
Day 4	5 (8.3)	24 (40.0)	31 (51.7)
Day 5	6 (10.0)	33 (55.0)	21 (35.0)
Day 6	8 (13.3)	38 (63.3)	14 (23.3)
Day 7	12 (20.0)	37 (61.7)	11 (18.3)

Comparison of day 1 and day 7: Table 6 compares mean values on day 1 and day 7. Mean sodium fell from 143.40 ± 8.05 to 140.66 ± 3.99 mEq/L ($p = 0.0195$), and the wide spread on day 1 narrowed by day 7. Mean potassium rose from 4.07

± 0.83 to 4.41 ± 0.50 mEq/L ($p = 0.0076$) and mean calcium from 9.10 ± 0.99 to 9.47 ± 0.67 mg/dL ($p = 0.0192$). Mean magnesium fell from 2.08 ± 0.38 to 1.92 ± 0.26 mg/dL ($p = 0.0098$), although both values were inside the reference range.

Table 6: Comparison of mean serum electrolytes and GCS on day 1 and day 7 (n = 60)

Parameter	Day 1, mean $\pm$ SD	Day 7, mean $\pm$ SD	Abnormal on day 1, n (%)	Abnormal on day 7, n (%)	p value
Sodium (mEq/L)	143.40 $\pm$ 8.05	140.66 $\pm$ 3.99	25 (41.7)	9 (15.0)	0.0195
Potassium (mEq/L)	4.07 $\pm$ 0.83	4.41 $\pm$ 0.50	19 (31.7)	5 (8.3)	0.0076
Calcium (mg/dL)	9.10 $\pm$ 0.99	9.47 $\pm$ 0.67	15 (25.0)	6 (10.0)	0.0192
Magnesium (mg/dL)	2.08 $\pm$ 0.38	1.92 $\pm$ 0.26	7 (11.7)	4 (6.7)	0.0098
GCS (score)	7.58 $\pm$ 2.66	10.42 $\pm$ 2.51	38 (63.3) severe	11 (18.3) severe	<0.0001

p values compare day 1 and day 7 means (t-test). Abnormal: value outside the reference range on that day (raised or low).

Electrolyte status and GCS on day 1: The association between electrolyte status and GCS category on day 1 is shown in Table 7 and Figure 2A. Of the 38 patients with severe injury, 15 (39.5%) were hypernatraemic and 7 (18.4%) hyponatraemic, so 57.9% had abnormal sodium. Among the 22 patients with mild or moderate injury, only 4 (18.2%) had abnormal sodium, and only 1 was hypernatraemic. The association between sodium status and GCS was significant ($p = 0.006$). Potassium showed a similar pattern: 17 of the 38 severe patients (44.7%) had abnormal potassium, 10 (26.3%) with hypokalaemia and 7

(18.4%) with hyperkalaemia, compared with 2 of 22 patients with lesser injury ($p = 0.027$). Calcium status was not associated with GCS on day 1 ($p > 0.99$); hypocalcaemia occurred at similar rates in the mild (25.0%), moderate (16.7%) and severe (18.4%) groups.

Magnesium status was also not significantly associated with GCS on day 1 ($p = 0.164$). Hypomagnesaemia was seen in 11.1% of moderate and 10.5% of severe patients, and the only patient with hypermagnesaemia had mild injury.

Table 7: Association of electrolyte status with GCS severity on day 1 (n = 60)

Electrolyte / GCS category	Raised, n (%)	Low, n (%)	Normal, n (%)	Any abnormality, n (%)
Sodium ($p = 0.006$)				
Mild (n = 4)	0 (0.0)	1 (25.0)	3 (75.0)	1 (25.0)
Moderate (n = 18)	1 (5.6)	1 (5.6)	16 (88.9)	2 (11.1)
Severe (n = 38)	15 (39.5)	7 (18.4)	16 (42.1)	22 (57.9)
Potassium ($p = 0.027$)				
Mild (n = 4)	1 (25.0)	0 (0.0)	3 (75.0)	1 (25.0)
Moderate (n = 18)	0 (0.0)	1 (5.6)	17 (94.4)	1 (5.6)
Severe (n = 38)	7 (18.4)	10 (26.3)	21 (55.3)	17 (44.7)
Calcium ($p = >0.99$)				
Mild (n = 4)	0 (0.0)	1 (25.0)	3 (75.0)	1 (25.0)
Moderate (n = 18)	1 (5.6)	3 (16.7)	14 (77.8)	4 (22.2)
Severe (n = 38)	3 (7.9)	7 (18.4)	28 (73.7)	10 (26.3)
Magnesium ($p = 0.164$)				
Mild (n = 4)	1 (25.0)	0 (0.0)	3 (75.0)	1 (25.0)
Moderate (n = 18)	0 (0.0)	2 (11.1)	16 (88.9)	2 (11.1)
Severe (n = 38)	0 (0.0)	4 (10.5)	34 (89.5)	4 (10.5)

Percentages are of patients in each GCS category on that day. p values: Fisher-Freeman-Halton exact test (3×3 table of hyper/hypo/normal by mild/moderate/severe).

Electrolyte status and GCS on day 7: On day 7 (Table 8; Figure 2B), abnormal values were concentrated in the 11 patients who remained in the severe category. Five of them (45.5%) had abnormal sodium (4 hypernatraemia, 1 hyponatraemia), compared with 4 of the 49 patients with mild or moderate injury (8.2%) ($p = 0.024$). Four severe patients (36.4%) had abnormal potassium, against 1 of 49 others ($p = 0.011$).

Calcium was abnormal in 4 severe patients (36.4%), 3 of them hypocalcaemic, and in 2 of 49 others ($p = 0.007$).

All 3 patients with hypomagnesaemia on day 7 were in the severe group (27.3% of that group), and magnesium status was associated with GCS ($p = 0.010$).

Table 8: Association of electrolyte status with GCS severity on day 7 (n = 60)

Electrolyte / GCS category	Raised, n (%)	Low, n (%)	Normal, n (%)	Any abnormality, n (%)
Sodium (p = 0.024)				
Mild (n = 12)	1 (8.3)	0 (0.0)	11 (91.7)	1 (8.3)
Moderate (n = 37)	2 (5.4)	1 (2.7)	34 (91.9)	3 (8.1)
Severe (n = 11)	4 (36.4)	1 (9.1)	6 (54.5)	5 (45.5)
Potassium (p = 0.011)				
Mild (n = 12)	0 (0.0)	0 (0.0)	12 (100.0)	0 (0.0)
Moderate (n = 37)	0 (0.0)	1 (2.7)	36 (97.3)	1 (2.7)
Severe (n = 11)	2 (18.2)	2 (18.2)	7 (63.6)	4 (36.4)
Calcium (p = 0.007)				
Mild (n = 12)	0 (0.0)	1 (8.3)	11 (91.7)	1 (8.3)
Moderate (n = 37)	1 (2.7)	0 (0.0)	36 (97.3)	1 (2.7)
Severe (n = 11)	1 (9.1)	3 (27.3)	7 (63.6)	4 (36.4)
Magnesium (p = 0.010)				
Mild (n = 12)	0 (0.0)	0 (0.0)	12 (100.0)	0 (0.0)
Moderate (n = 37)	1 (2.7)	0 (0.0)	36 (97.3)	1 (2.7)
Severe (n = 11)	0 (0.0)	3 (27.3)	8 (72.7)	3 (27.3)

Percentages are of patients in each GCS category on that day. p values: Fisher-Freeman-Halton exact test (3 × 3 table of hyper/hypo/normal by mild/moderate/severe).

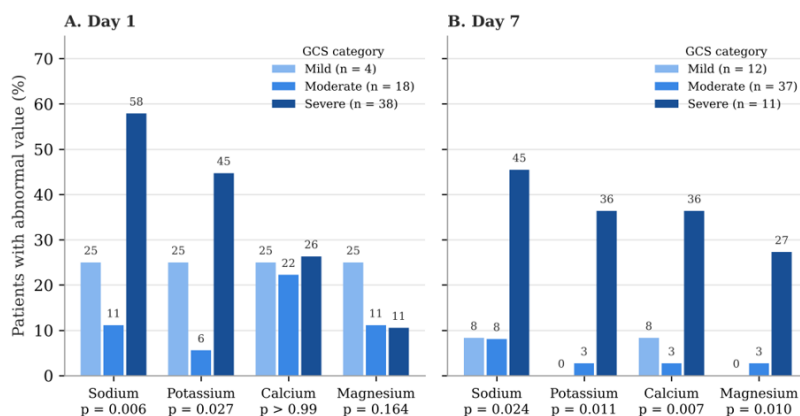


Figure 2: Percentage of patients with an abnormal electrolyte value (raised or low) in each GCS category on day 1 (A) and day 7 (B). Numbers above bars are percentages of patients in that GCS category. p values from the Fisher-Freeman-Halton exact test (Tables 7 and 8)

Discussion

In this cohort of 60 adults with TBI followed daily through the first week of intensive care, half of the patients had at least one abnormal sodium value, more than a third had abnormal potassium, and hypernatraemia was the commonest single disturbance. Abnormal values were most frequent in the first days after admission and became less common as GCS improved. On day 1, sodium and potassium status were associated with injury severity, whereas calcium and magnesium were not; by day 7, abnormalities of all four electrolytes were concentrated in the small group of patients who were still severely injured.

The demographic profile matches what is known about TBI in India, where road traffic injury accounts for the majority of cases [3]. Our patients were mostly men of working age (mean age 41 years), and 85.0% were injured on the road. The

male predominance (95.0%) is higher than that reported in other ICU series. In 70 patients with isolated TBI in an ICU in Srinagar, Para and colleagues found 65.7% men, a mean age of 35.5 years and road traffic accidents in 43.6%, with falls from height in 35.7% [16]. Rafiq and colleagues reported 59.1% men among 215 patients with severe head injury in Islamabad [17], and Deveduthras and colleagues 77.7% men among 184 patients in Durban [18]. The very high proportion of men in our cohort may reflect patterns of travel and work in the region, and partly the small sample. Subdural haemorrhage was the commonest CT finding in our series (61.7%), as in the series of Pin-On and colleagues, where 51% of patients needing emergency craniotomy had subdural and 36% extradural haematoma [19]. Paiva and colleagues found that sodium disorders were more common with subdural haematoma, intracerebral haematoma and diffuse axonal injury, and more

common with diffuse injury than with contusion ($p = 0.022$) [20]. Our sample was too small to examine electrolyte disturbance by lesion type.

The frequency of electrolyte disturbance in our study falls within the wide range reported elsewhere, and the differences between studies are largely explained by the patients they enrolled. Rafiq and colleagues, who included only severe injuries (GCS below 8) and monitored electrolytes twice daily for a week, found hypernatraemia in 65.1% and hypokalaemia in 36.7%, with little change in calcium and magnesium [17]. Deveduthras and colleagues reported abnormal sodium in 68.4% of patients with moderate to severe TBI, almost equally divided between hypernatraemia (35.3%) and hyponatraemia (33.1%) [18]. In the prospective study of Paiva and colleagues, 45% of 80 patients had a sodium disorder, 25% with hypernatraemia and 20% with hyponatraemia [20]. Our figures (51.7% overall; 33.3% hypernatraemia and 18.3% hyponatraemia) are closest to those of Paiva and colleagues, whose exclusion criteria resembled ours, and lower than those of studies restricted to severe injury. The relative order of disturbances is not the same in all settings. Pin-On and colleagues found hypokalaemia to be the commonest abnormality, in 65.5% of patients undergoing emergency craniotomy [19], which contrasts with our finding that sodium was more often deranged than potassium.

Several mechanisms could explain why hypernatraemia outnumbered hyponatraemia. All of our patients received normal saline, one-third received mannitol and 18.3% received 3% saline, and osmotherapy is a recognised cause of a rising sodium [8]. Fever, insensible losses and limited free water in patients with a depressed level of consciousness add to it. Central DI is a further cause in the more severely injured. Agha and colleagues found acute DI in 21.6% of survivors of moderate or severe TBI, more often after severe injury [7], and Maggiore and colleagues found hypernatraemia most often in patients with suspected central DI, who also had more severe injuries and higher ICU mortality [10]. Among the 65 hypernatraemic patients of Deveduthras and colleagues, the cause was dehydration in 80%, DI in 10.7% and hyperosmolar therapy in 9.3%; among the 61 hyponatraemic patients, it was fluid overload in 77.1%, SIADH in 18% and cerebral salt wasting in 4.9% [18]. We did not measure urine osmolality, urine sodium or ADH, so we cannot assign a cause to each case, but these figures suggest that much of the sodium disturbance seen in the ICU is related to fluid management and can be prevented.

Most sodium abnormalities in our study were present on day 1, and their frequency fell steadily

after day 5. Vedantam and colleagues found that 79.3% of hypernatraemia in severe TBI was detected within the first week, and 46% within 72 hours of admission [21]. Paiva and colleagues detected 53% of sodium disorders in the first blood sample [20]. Harrois and colleagues, using 6-hourly sodium values in 240 patients with severe TBI, reported hypernatraemia in 64% and hyponatraemia in 24%; the day-to-day variability of sodium peaked at a median of 2 days after admission, fell progressively over the first week, and was independently associated with 28-day mortality (HR 1.27) [22]. Our finding that the SD of serum sodium halved between day 1 (8.05) and day 7 (3.99) mEq/L is consistent with this, and suggests that the first three to five days are when daily or more frequent sodium measurement is most useful.

Sodium status was clearly related to injury severity. On day 1, 57.9% of patients with severe injury had abnormal sodium compared with 18.2% of those with mild or moderate injury, and on day 7 the corresponding figures were 45.5% and 8.2%. Meng and colleagues found hyponatraemia in 56 of 136 patients with moderate or severe TBI and identified a GCS of 8 or less, cerebral oedema and basal skull fracture as independent risk factors [23]. Maggiore and colleagues linked hypernatraemia to more severe brain injury [10]. The same association appears in outcome studies: Vedantam and colleagues reported hazard ratios for death of 3.4, 4.4 and 8.4 for mild, moderate and severe hypernatraemia in 588 patients with severe TBI [21]; Hoffman and colleagues, using a national database of more than 90,000 patients, found that hypernatraemia was associated with higher in-hospital mortality (OR 1.51, 95% CI 1.39 to 1.65) and a longer mean stay (23.65 versus 12.12 days) [24]; and Li and colleagues showed mortality rising steeply with the degree of hypernatraemia [11]. Hyponatraemia has likewise been tied to longer stays and unfavourable outcome [9]. Our study was not designed to test whether sodium disturbance causes a worse course or simply marks a more severe injury; both are plausible, and the two are hard to separate in observational data. Hypokalaemia was the second commonest disturbance in our study (23.3%), and most cases were present early. This agrees with Pomeranz and colleagues, who found hypokalaemia within hours of severe head injury and attributed it to catecholamine-driven intracellular shift of potassium [12], and with Wu and colleagues, who observed the peak of severe hypokalaemia between 24 and 96 hours [13]. Rafiq and colleagues found hypokalaemia in 36.7% of patients with severe injury [17], a higher rate than ours, which again fits their more severe case mix. In our cohort, mannitol-induced diuresis and beta-2 agonist nebulisation may also have contributed. On day 1,

26.3% of severely injured patients were hypokalaemic, against 5.6% of moderate and none of the mild patients, and the association with GCS was significant on both day 1 and day 7. Pomeranz and colleagues, by contrast, found no correlation between serum potassium and admission GCS [12], but all of their patients already had a GCS of 7 or less, which leaves little room to detect a gradient. Wu and colleagues found that both a lower GCS and a lower potassium predicted death [13]. Hyperkalaemia in 15.0% of our patients was unexpected; it may reflect haemolysed samples, tissue injury, acidosis or blood transfusion, none of which we recorded systematically.

Hypocalcaemia occurred in 20.0% of patients. On day 1 it was evenly distributed across GCS categories and showed no association with severity, but on day 7 three of the four hypocalcaemic patients were in the severe group ($p = 0.007$). Studies that measured ionised calcium give some support to the idea that calcium follows the course of the injury. Viñas-Rios and colleagues found that ionised calcium on the third day after moderate or severe TBI separated patients with poor outcome from the rest, with a cut-off of 1.11 mmol/L giving an OR of 6.45 for death or disability [25]. Cernak and colleagues found that plasma calcium stayed low throughout the first week only in patients with severe injury [15]. The experimental basis is the shift of calcium into injured cells described by Weber [14]. We measured total rather than ionised calcium and did not correct it for albumin, which probably weakened any association on day 1, when albumin and acid-base status are most variable.

Magnesium was the most stable electrolyte, with hypomagnesaemia in 13.3% of patients. Rafiq and colleagues also found little change in magnesium [17]. Nayak and colleagues, in contrast, found a low serum magnesium (below 1.3 mEq/L) in 58% of 72 patients with severe TBI at admission, and hypomagnesaemia was independently associated with poor neurological outcome at six months (OR 2.1) [26]. Their cut-off and patient group differ from ours, which explains much of the gap. On day 1 we found no significant association between magnesium and GCS ($p = 0.164$), but on day 7 all three patients with hypomagnesaemia were among those still severely injured. Cernak and colleagues reported a similar time pattern, with magnesium recovering by day 3 after mild injury but remaining low for a week after severe injury [15]. In children, Mendez and colleagues found that total plasma magnesium fell after TBI of any severity, while ionised magnesium fell only after severe injury and returned to normal within 24 hours [27]. Total serum magnesium, which we measured, may therefore miss short-lived changes in the ionised fraction.

Across all four electrolytes, the number of patients with abnormal values fell between day 1 and day 7 while mean GCS rose by almost three points. Both changes are what one would expect as patients recover and receive protocol-based correction, and we cannot say from these data that correcting the electrolytes improved the GCS. The day 7 analysis does show, however, that the patients whose consciousness had not improved were also those whose electrolytes remained abnormal. For practice, this supports daily measurement of sodium and potassium in every patient with moderate or severe TBI during the first week, with particular attention to patients receiving osmotherapy, and continued monitoring of calcium and magnesium in those who remain in the severe category.

The study has several limitations. The sample was small and drawn from a single centre, which limits precision, particularly for the less common disturbances. Not all patients were admitted on the day of injury, and some had received fluids and drugs at a peripheral hospital, so day 1 of the study did not always correspond to day 1 after injury. Patients who died within seven days were excluded, which removes the most severe cases and probably underestimates the frequency of disturbance. We did not record daily fluid volumes, urine output, urine osmolality, urine sodium or specific gravity, and so could not distinguish SIADH, cerebral salt wasting and DI. Calcium and magnesium were measured as total rather than ionised concentrations. Patients were not followed beyond day 7, so the relation between electrolyte disturbance and longer-term outcome could not be examined. Finally, patients with systemic disease, endocrine disorders and other causes of electrolyte disturbance were excluded, which improves internal validity but means the results may not apply to older patients with comorbidities.

Conclusion

Electrolyte disturbance was common in adults admitted to the ICU with traumatic brain injury. Sodium was the electrolyte most often affected, and hypernatraemia was the most frequent single abnormality, followed by hypokalaemia, hypocalcaemia and hyponatraemia. Magnesium changed least. Most disturbances were present at or soon after admission and became less frequent over the first week as patients received protocol-based treatment and their GCS improved. Sodium and potassium abnormalities were associated with severe injury from the first day, while calcium and magnesium abnormalities were associated with GCS only by day 7, when they were concentrated in patients who remained severely injured. These findings support daily measurement of sodium and potassium during the first week of ICU care for every patient with moderate or severe TBI, closer

surveillance of patients receiving mannitol or hypertonic saline, and continued checking of calcium and magnesium in patients whose GCS does not improve. Larger multicentre studies that record fluid balance, urinary indices, ionised calcium and magnesium, and longer-term outcome are needed to establish whether early detection and correction of these disturbances changes neurological recovery.

Declarations

Ethical approval: Approved by the Institutional Ethics Committee (Human), Assam Medical College, Dibrugarh. Written informed consent was obtained from each patient's guardian.

Conflicts of interest: None declared.

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