ORIGINAL ARTICLE

JIACM 2026; 27 (1): 17-22

Aetiological Spectrum of Hospital-Acquired Hypernatraemia

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Abstract

***Background:** In critically ill, hospitalised patients, hypernatraemia has been an independent predictor of mortality. Hospital acquired hypernatraemia (HAH) is a frequently overlooked entity and knowledge of common risk factors for hypernatraemia can help early identification of HAH and fluid management to be modified accordingly.*

***Methods:** This cross-sectional, observational study enrolled 100 adult patients who developed hypernatraemia (Na^+ >145 mEq/L) after 48 hours of admission. Amount of enteral feed, its mode of administration and net tonicity of intravenous (IV) fluids were calculated. Administration of sodium containing drugs were recorded. Factors leading to renal and extrarenal free water loss were assessed. Patients were classified as having mild hypernatraemia (146 - 149 meq/L), moderate (150 - 159 meq/L) and severe hypernatraemia (>160 meq/L). The assessment of risk factors in patients with mild (Group I) vs moderate + severe hypernatraemia (Group II) were done.*

***Results:** The mean age of the study cohort was 52.83 ± 16.9 years with M: F ratio of 3.34. Hypertension was the most common co-morbidity (23%) with neurological diseases (40%) being the most common reason for hospital admission. 42% patients developed hypernatraemia on day 3, 36% on day 4 and 22% after 5 days. The mean serum sodium levels were 150.97 ± 4.88 mEq/L. 51% had mild hypernatraemia, 42% had moderate and 7% had severe hypernatraemia. Among the various causes of hypernatraemia, hypertonic fluids and sodium containing drugs contributed in 63% and 75% of patients respectively. Extrarenal water loss and factors with potential to cause renal water loss were observed in 51% and 43% of patients respectively. 78% of patients did not have free access to water.*

***Conclusion:** HAH is multifactorial and a close vigilance on various risk factors can aid in risk stratification and institution of prompt measures to prevent hypernatraemia and improve quality of health care.*

***Key words:** Hypernatraemia, Osmolality, intravenous fluids, drugs.*

Introduction

Sodium and water disorders are frequently seen in critically ill, hospitalised patients with hypernatraemia as an independent predictor of mortality[1]. It has been classified as community or hospital acquired hypernatraemia (CAH or HAH) with HAH defined as serum sodium concentration above 145 mEq/L occurring during hospitalisation among patients having normal serum sodium on admission[2]. The reported prevalence of HAH varies from 1 - 6% which is higher than reported for CAH (0.2%) stressing an iatrogenic component in its evolution[3-7].

In critically ill, hospitalised patients, hypernatraemia develops because of gain of sodium, due to loss of free water from the body or from combination of both. Gain of sodium usually occurs due to administration of hypertonic intravenous fluids, sodium containing drugs. Secondly, loss of free water from body can occur due to renal or extrarenal causes contributing to hypernatraemia. Renal free water loss may be accounted by various factors, viz., diabetes insipidus, hyperglycaemia, use of loop diuretics or mannitol whereas extrarenal free water loss can occur via several routes viz., enteral fluid loss (diarrhoea/vomiting) or increased insensible water losses (sweat or respiratory losses as seen during fever or mechanical ventilation respectively)[8]. Thirst is a protective mechanism against development of hypernatraemia which is often supressed or rendered ineffective by inadequate access to free water owing to underlying medical condition viz., cerebrovascular accidents, acute pancreatitis, etc.

HAH is frequently overlooked by treating physicians amidst management of more urgent medical issues of patients. The knowledge of common clinical risk factors for hypernatraemia can help identifying HAH early and fluid management to be modified accordingly. Literature is limited on this topic from this part of world and moreover had shown varied factors in different settings; so with this study, we planned to explore the aetiological causes of HAH at our tertiary care centre.

Material and Methods

The study was a cross-sectional, observational study carried out at the Department of Medicine, Pt. B.D. Sharma

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PGIMS, Rohtak from November 2023 to October 2024 and a total of 100 adult patients who developed hypernatraemia (Na^+ >145 mEq/L) after 48 hours of admission were included in the study. The demographic profile and relevant clinical details including day on which hypernatraemia developed after hospitalisation, clinical diagnosis and presence of other co-morbidities were noted. Serum sodium levels were estimated using ion selective electrodes. Normal serum osmolality was taken between 280 to 295 mOsm/kg[9]. Amount of enteral feed and its mode of administration (Ryles tube or oral) was noted. Net tonicity of the parenteral fluids administered over prior 48 hours was calculated after dividing total number of osmoles infused by total volume of fluid administered. Concomitant potassium chloride administration was also considered for calculating tonicity of fluids. Administration of commonly used sodium containing drugs, viz., antibiotics (Ampicillin, Amoxycillin/clavulanic acid, Piperacillin, Ceftriaxone, Cefazolin, Ceftazidime, Ciprofloxacin), antifungals (Fluconazole, Voriconazole, Foscarnet), antiepileptics (Sodium Valproate, Phenytoin) and sodium bicarbonate (injection or tablets) over the 48 hours preceding the development of hypernatraemia were recorded. Extrarenal free water loss due to diarrhoea (stools of loose consistency with frequency more than 4 times daily), vomiting, fever (oral temp >38^0 C) was assessed. Factors leading to renal free water loss (glycosuria, mannitol, loop diuretics) in 48 hours preceding the development of hypernatraemia were recorded. Daily urine output of the patients was recorded. Polyuria was defined as 24-hour urine volume exceeding 3 L/day[9]. The Study was approved by the institutional Ethical Committee vide letter no BREC/23/TH-Medicine-13 dt 05.10.2023.

Definitions

Hypernatraemia: Patients with serum sodium levels of > 145 meq/L were diagnosed to have hypernatraemia and were further divided into three subgroups having mild (145 - 149 meq/L), moderate (150 - 159 meq/L) and severe (>160 meq/L) hypernatraemia[10].

Tonicity of Fluids: Intravenous fluids administered in 48 hours preceding the development of hypernatraemia were classified based on calculated net tonicity (Hypertonic: >/300/mOsmol/kg; Isotonic: 280 - 300/mOsmol/kg; Hypotonic </280/mOsmol/kg).

Statistical analysis

The data was recorded in predesigned proformas. The data entry was done in Microsoft Excel for windows and data analysis was done using Quickcals (GraphPad Software; San Diago, CA). The presentation of categorical variables was done in the form of number and percentage (%). For the quantitative data, the normally distributed variables were expressed as mean ± standard deviation (SD) and the continuous variables with skewed distribution as median (interquartile range).

Results

Demographic Profile of Patients (n=100)

The study participants age ranged between 18 to 86 years. The mean age of the cohort was 52.83 ± 16.9 years with male: female ratio of 3.34. Hypertension was the most common co-morbidity (23%) with neurological diseases (40%) being the most common reason for hospital admission. 42% patients developed hypernatraemia on day 3 as compared to 36% on day 4 and 22% developing hypernatraemia after 5 days of hospital stay. The trends have been shown in Table I.

Table I: Baseline parameters and time to develop hypernatraemia in patients.

Parameters	N = 100
Age (Mean + SD)	52.83 ± 16.9 years
Gender (M: F)	3.34
Co-morbidities	
Hypertension	23
Chronic liver disease	11
Diabetes mellitus	11
Neurological diseases	9
Chronic kidney disease	7
Pulmonary diseases	6
Cardiovascular diseases	4
Others	7
Multiple comorbidities	18
Reason for Admission	
Neurological disease	40
Gastrointestinal tract and Liver disease	23
Respiratory disease	10
Renal disease	6
Cardiovascular disease	3
Others	18
Time of Onset of Hypernatraemia (Days)	
3	42
4	36
>5	22

Serum electrolytes in study population

The serum sodium levels ranged 146 - 168 mEq/L with a mean value of serum sodium level being 150.97 ± 4.88 mEq/L. Fifty one patients had mild hypernatraemia, 42 had moderate and 7 had severe hypernatraemia as shown in Table II, (Fig. 1a and 1b).

Table II: Grades of hypernatraemia.

Grades of Hypernatraemia	No. of Subjects (100)
Mild hypernatraemia (146 - 149 meq/L)	51
Moderate hypernatremia (150 - 159 meq/L)	42
Severe hypernatremia (>160 meq/L)	7

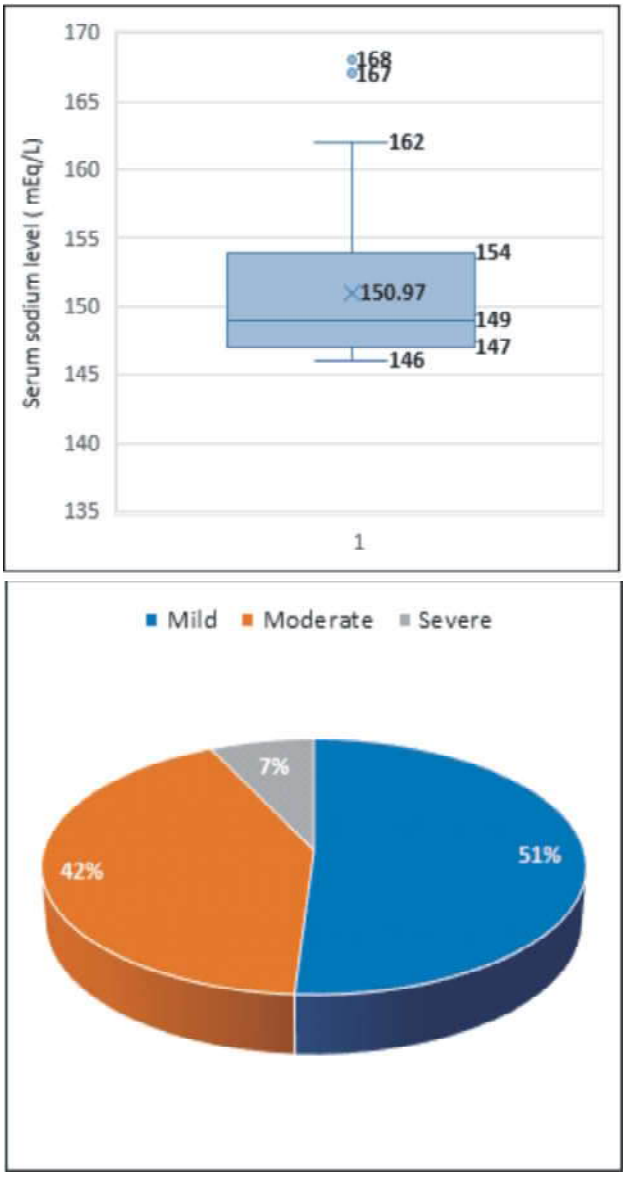

Fig. 1a, 1b: *Serum sodium levels in patients.*

Risk factors for hospital acquired hypernatraemia (HAH) in study population

Hypertonic IV fluids and sodium containing drugs were used in 63% and 75% of patients respectively. Extrarenal water loss and factors with potential to cause renal water loss as risks were observed in 51% and 43% of patients respectively. 78% of patients did not have free access to water as shown in Table III.

Table III: Risk factors for HAH.

IV Fluids	100
Hypertonic (>300 mOsm/kg)	63
Isotonic (280 - 300 mOsm/kg)	19
Hypotonic (<280 mOsm/kg)	16
No IV fluids	02
Sodium Containing Drug	75
Antibiotics	68
Antiepileptics	15
Sodium bicarbonate	13
More than one sodium containing drug	21
Extra renal Water Loss	51
Fever	41
Gastrointestinal tract loss	18
Diarrhoea	11
Vomiting	7
>1 factor	8
Factors having potential to cause renal water loss	43
Mannitol	20
Loop diuretic	18
Glucose	10
Diabetes insipidus	0
More than one factor	5
Free access to water	100
Yes	22
No	78

Risk factors among different grades of hypernatraemia

Fifty one patients had mild hypernatraemia and 49 patients had moderate to severe hypernatraemia. Presence of various risk factors among different subgroups has been shown in Table IV, (Fig. 2).

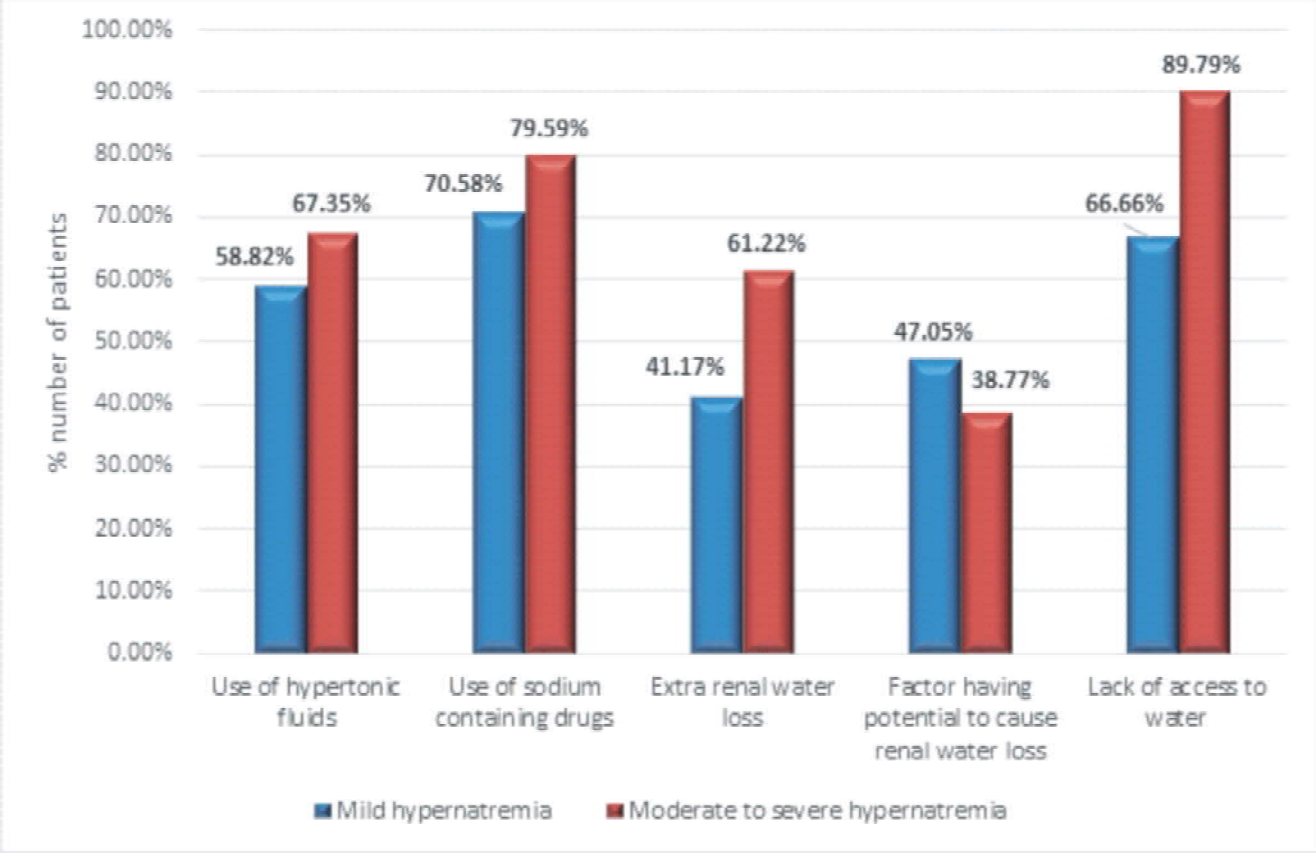

Fig. 2: *Various risk factors among different grades of hypernatraemia.*

Table IV: Risk factors among different grades of hypernatraemia

Risk Factor	Mild Hypernatraemia (n = 51)	Moderate + Severe Hypernatraemia (n = 49)
Use of hypertonic fluids	30 (58.82%)	33 (67.35%)
Use of sodium containing drugs	36 (70.58%)	39 (79.59%)
Extra renal water loss	21 (41.17%)	30 (61.22%)
Factors with potential to cause renal water loss	24 (47.05%)	19 (38.77%)
Lack of access to water	34 (66.66%)	44 (89.79%)

Discussion

Hypernatraemia in critically ill hospitalised patients has a high mortality rate than patients with normal sodium levels (43% *versus* 24%)[11]. Plasma sodium level reflects ratio of sodium and water in the body with hypernatraemia being actually an indicator of relative deficiency of free water compared to sodium[12]. As many critically ill patients have impaired level of consciousness, their water balance is no longer regulated by thirst but is ill-managed, often by the physician or caretaker, leading to iatrogenic hypernatraemia. Attention to risk factors associated with development of HAH has the potential to prevent its occurrence, decrease mortality rates and improve quality of healthcare. With this study, we tried to explore various clinical risk factors for development of HAH.

The average age of patients was 52.8 ± 16.9 years with a male predominance. More than half of the patients (57%) had pre-existing chronic medical illness. The reason for hospitalisation, organ system involvement showed wide diversity, with predominance of neurologic diseases (40%). The mean duration of hospital stay before the onset of hypernatraemia was 4.27 ± 1.83 days. These observations get strength from other study showing average onset of hypernatraemia on day 5.9 ± 4.3 of ICU stay with almost all patients requiring 2 days to develop hypernatraemia[8].

The mean value of serum sodium level was 150.97 ± 4.88 mEq/L. About half of the study participants (51%) had mild hypernatraemia and this finding can be accounted by the fact that fluid management is a dynamic and ongoing process rather than being a single intervention. We hypothesize that the treating physicians increased the number of hypotonic fluids after looking at the trends of serum sodium thereby preventing the development of moderate-to-severe hypernatraemia but the amount was

not sufficient for the prevention of mild hypernatraemia.

Intravenous fluids were given to 98% of patients with use of hypertonic IV fluids in 63% patients, which is much higher than reported from another study using IV hypertonic solutions in only 27% patients preceding the onset of hypernatraemia[8]. Normal saline and dextrose normal saline (DNS) were the predominant fluids used (osmolality of 308 mOsmol/kg), thus making them hypertonic as compared to normal serum osmolality of 280 - 295 mOsmol/kg[9,10,12]. Further potentiating HAH was the use of potassium chloride, which was added to intravenous fluids in 38% of patients to correct either hypokalaemia or to meet daily requirement. Addition of potassium chloride to intravenous fluids increased the osmolality of intravenous fluids resulting in osmolality of IV fluids in hypertonic range in 86.8% patients. Previous studies had also reported increased tonicity of IV fluids with addition of potassium[8,14], further highlighting importance of potassium as iatrogenic cause of HAH.

75% patients were given sodium containing drugs which included antibiotics (68%), antiepileptics (15%) and sodium bicarbonate (13%). Since the list of sodium containing drugs is vast and moreover it is difficult to quantify sodium content of these drugs; we could not find any study deciphering the exact role of this class of drugs in causation of HAH. However, causation of HAH with use of sodium bicarbonate has been studied earlier with usage ranging from 12.5 - 18% of patients prior to the onset of hypernatraemia[8,15,16]. The use of sodium bicarbonate was in 13% of patients in our study.

Extrarenal water losses prior to development of hypernatraemia were observed in 51% patients. Fever was recorded in 41% while increased gastrointestinal tract fluid losses were seen in 18%. These findings were similar to a study reporting fever in 56% and enteral losses in 40% patients developing HAH[17]. An interesting fact was that in 4% of cases, diarrhoea was caused by overzealous use of lactulose in hepatic encephalopathy patients and we emphasize on its judicious use to cause only 3 - 4 semisolid stools per day as described earlier in a study[18].

Average urine output was 1001.3 ± 394.87 ml in the study population. None of the patients had polyuria, which is in sharp contrast to a previous study reporting polyuria in 38% patients (diuretics in 50%, osmotic diuresis in 30% and diabetes insipidus in 20%)[8]. In our study, none of the patients had diabetes insipidus. Loop diuretics were used in 18%, mannitol in 20% and 10% patients had glycosuria. Loop diuretics have been shown to cause defect in urine concentrating abilities of kidneys during hypernatraemia, however as we did not quantify urine osmolality in our study, so we cannot compare our findings with previous data. However, we stress that daily assessment of water balance in hospitalised ill patients is crucial. Urine electrolyte free water should be calculated and added to daily fluid requirement of patients to replenish free water loss, especially in patients receiving diuretics and mannitol to prevent hypernatraemia.

Enteral feeding was present in 62% patients and 38% patients had no enteral intake. Liquid feed was given to patients either orally or through Ryles tube. The average enteral intake in these patients was 424.75 mL and 88.7 % of these patients received enteral feed below 1000 mL. The details on tonicity of enteral feed were not recorded, so the current study cannot make comment on free water intake via enteral feed.

78% of patients in this study cohort lacked free access to water. Thirst is a powerful protective mechanism against hypernatraemia and lack of access to water might have contributed to the development of hypernatraemia in these patients[19]. Palevsky *et al* reported lack of access in 86% of patients having hospital acquired hypernatraemia[17]. In our study, the reason behind lack of free access to water was either impaired thirst perception due to altered mental status or prohibited enteral feeding due to enteral diseases. All patients with GCS score below 15 lacked free access to water which highlights the tendency of treating physicians to preclude oral intake in critically ill patients with possible high-risk of aspiration, serious illness or sepsis[12]. Further complicating the scenario, out of 22 patients who had free access to water, only 5 patients had enteral intake above 1000 mL which might be attributed to loss of appetite and nausea from illness or medications side effects. The current study highlights the early recognition of at-risk patients (patients with low GCS) and appropriate free water administration to be made an integral part of comprehensive continuum of care for critically ill patients.

The study had some inherent limitations. It was an observational study, hence causative association of risk factors with development of hypernatraemia cannot be established concretely. Due to lack of standardisation of enteral feed, only amount of enteral feed was evaluated and free water content of feed cannot be commented. Since renal concentrating defect (urine osmolality) was not assessed, only the presence of risk factors which can cause renal free water loss were recorded and their contribution to HAH cannot be comment upon concretely.

In conclusion, we stress that clinicians need to consider ongoing hypotonic fluid loss from renal or extrarenal route, judicious use of sodium containing drugs and appropriate amount of electrolyte free water to prevent development of hypernatraemia. Moreover, oral intake in critically ill patients should be encouraged and iatrogenic suppression

of protective thirst mechanisms needs to be avoided. In resource-limited hospital settings where daily calculation of tonicity balances in all patients is not possible, knowledge of these clinical factors can aid in risk stratification and treatment planning to prevent hypernatraemia and improve quality of healthcare.

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The following particulars regarding the ownership of the **'JOURNAL, INDIAN ACADEMY OF CLINICAL MEDICINE'** are published as called for by Rule 8 of the Registration of Newspaper (Central) 1956.

1.	Place of Publication	–	108, SFS Flats, Ashok Vihar, Phase-4, New Delhi - 110 052.
2.	Periodicity of Publication	–	Quarterly
3.	Printer's Name	–	Dr. Sumeet Singla
	Nationality	–	Indian
	Address	–	108, SFS Flats, Ashok Vihar, Phase-4, New Delhi - 110 052.
4.	Publisher's Name	–	Dr. Sumeet Singla
	Nationality	–	Indian
	Address	–	108, SFS Flats, Ashok Vihar, Phase-4, New Delhi - 110 052.
5.	Editor's Name	–	Dr. Sumeet Singla
	Nationality	–	Indian
	Address	–	108, SFS Flats, Ashok Vihar, Phase-4, New Delhi - 110 052.

6. Name and address of individuals who own the newspaper and partners or shareholders holding more than one per cent of the total capital.
   – Indian Association of Clinical Medicine, Headquarters: Post-graduate Department of Medicine, Sarojini Naidu Medical College, Agra - 282 002 (U.P.)

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