Risk factors for hospital-acquired hypernatremia among critically ill medical patients in a setting utilizing a preventive free water protocol: Do we need to do more?

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Abstract

Context: Hospital-acquired hypernatremia (HAH) is a frequent concern in critical care, which carries high mortality. Aims: To study the risk factors for HAH in settings that practice a preventive protocol. Settings and Design: Two tertiary-care hospitals. Prospective observational study design. Materials and Methods: Patients aged >18 years admitted for an acute medical illness with normal serum sodium and need for intensive care >48 h formed the study population. Details of the basic panel of investigations on admission, daily electrolytes and renal function test, sodium content of all intake, free water intake (oral, enteral and intravenous) and fluid balance every 24 h were recorded. Individuals with serum Na 140-142 meq/l received 500 ml of free water every 24 h, and those with 143-145 meq/l received 1000 ml free water every 24 h. Statistical Analysis Used: Risk factors associated with HAH was analysed by multiple logistic regression. Results: Among 670 study participants, 64 (9.5%) developed HAH. The median duration of hypernatremia was 3 days. A total 60 of 64 participants with HAH had features of renal concentrating defect during hypernatremia. Age >60 years (P = 0.02), acute kidney injury (AKI) on admission (P = 0.01), mechanical ventilation (P = 0.01), need for ionotropes (P = 0.03), worsening Sequential Organ Failure Assessment (SOFA) score after admission (P < 0.001), enteral tube feeds (P = 0.002), negative fluid balance (P = 0.02) and mannitol use (P < 0.001) were the risk factors for HAH. Mortality rate was 34.3% among hypernatremic patients. Conclusions: The study suggests that administration of free water to prevent HAH should be more meticulously complied with in patients who are elderly, present with AKI, suffer multi-organ dysfunction, require mechanical ventilation, receive enteral feeds and drugs like mannitol or ionotropes.

Keywords: Critical care, hospital, hypernatremia, mortality

Introduction

Hospital-acquired hypernatremia (HAH) is a frequent concern in critical care since 93% of HAH occur in an intensive care unit.[1] From a physiologist viewpoint, HAH can occur on account of a negative water balance as during decreased free water intake, increased renal water diuresis and gastrointestinal hypotonic fluid loss, or as a result of a positive sodium balance as during salt-rich enteral feeds, hypertonic enemas or drugs.[2,3] However, inadequate free water intake is the most consistent risk factor associated with hypernatremia acquired in the community or after hospitalization.[1,4]
Formulae exist to conclusively evaluate the amount of free water required to lower serum Na when it increases above 145 meq/L. However, they fail to discuss strategies to calculate free water intake when serum Na is between 140 and 145 meq/L. Although specific recommendations on the volume of free water administration among critically ill patients is not available, principles in critical care management will concur with a policy that recommends increase in free water administration when serum Na shows a rising trend. Reports of inadequate free water administration leading to HAH often help physicians to constantly reassess free water intake when observing a rising trend in serum sodium. But this effort has not eliminated the problem of hypernatremia among hospitalized patients. This study was initiated to identify risk factors for HAH in settings that practice a preventive free water protocol with a core objective of identifying a set of clinical parameters that probably need a better management approach to prevent or perhaps lessen the occurrence of this disorder.

Materials and Methods

Consecutive patients aged >18 years admitted for an acute medical illness under one of the study authors in the multi-disciplinary intensive care units of two tertiary-care hospitals in Chennai from January 2008 to May 2011 formed the study population. Participants were required to have normal serum sodium on admission (135-145 meq/l) and need for intensive care >48 h.

After enrollment the participants were evaluated with a clinical examination and a panel of investigations, which included complete blood count, blood sugar, serum creatinine, blood urea nitrogen, serum sodium, potassium, chloride, bicarbonate, calcium, phosphorus, magnesium, arterial blood gas analysis, liver function tests, ECG, chest X-ray and ultrasound. Electrolytes were estimated using ion-selective electrodes. Patients on mechanical ventilation were assessed for clinical evidence of focal sepsis, advanced liver disease, heart failure, poisoning, cerebro-vascular disease and airway obstruction among those who were alert during sedation vacation. A restricted assessment was made in patients who were sedated. Patients who had altered behavior were assessed for possible reasons (imbalance in electrolytes, uremia, hepatic encephalopathy, cerebro-vascular disease, hypoxia, hypercarbia, acidosis, hyperthermia, etc). Renal function test and electrolytes were monitored daily and capillary blood glucose was monitored at 2- to 8-hourly intervals depending on trends in glucose levels. Additional tests were made as per clinical indication. Sequential Organ Failure Assessment (SOFA) score was recorded daily. HAH was defined as serum sodium ≥146 meq/l occurring after 24 h of hospitalization among patients who had normal serum sodium on admission.

Details of a basic panel of investigations on admission, daily electrolytes and renal function test, sodium content of all intake (intravenous fluids, medications and oral or enteral feeds), free water intake (oral, enteral and intravenous) and fluid balance were recorded every 24 h. Urine concentrating defect was defined as urine osmolality <700 mOsm/kg during HAH.

Patients received intravenous fluids or feeds (oral or enteral feeds through a naso-gastric tube) as per practice of the study authors. Patients with serum Na 140-145 meq/L were administered free water as per our preventive protocol in which individuals who had a serum sodium of 140-142 meq/l on admission or during hospital stay received 500 ml of free water every 24 h of hospitalization among patients who had normal serum sodium every 24 h (100 ml q 4 hour through a naso-gastric tube till the target of 500 ml was reached or as 500 ml of 5% dextrose over 5 h) and those with 143-145 meq/l received 1000 ml of free water every 24 h (100 ml q 2 hour through a naso-gastric tube till the target of 1000 ml was reached or as 1000 ml of 5% dextrose over 10 h) to avoid further increment in serum sodium. This policy was based on a consensus between our study investigators, which was based on two assumptions. First, a patient with low normal Na (135-139 meq/l) has an intact renal concentrating ability and will retain appropriate water due to centrally mediated hormonal effects on kidneys and will avoid occurrence of hypernatremia. Second, a patient with high normal serum Na (140-145 meq/l) has a tendency for possible renal hypotonic fluid loss and needs supplemental free water to prevent further rise in serum Na.

This policy of free water administration to avoid hypernatremia in patients with high normal serum sodium was continued during the study on account of ethical reasons and to facilitate identification of reasons leading to failure of this preventive strategy. Informed consent was obtained from the closest relative of the study participants. The institutional review board of the study centers approved the protocol.

Continuous variables were expressed as mean ± SD if normally distributed and as mean or median with range for skewed distribution. Categorical variables were expressed as number (%). Possible risk factors (age, gender, diabetes mellitus, other pre-existing chronic...
medical illness, AKI on admission, hyperglycemia, sepsis, mechanical ventilation, hypoalbuminemia, hypokalemia, worsening SOFA score, need for ionotropes, enteral feeds, volume of free water administered 24 h prior to Na estimation, salt intake 24 h prior to Na estimation, negative fluid balance, mannitol use and frusemide use) associated with HAH were analyzed by multiple logistic regression preceded by univariate analysis. Correlation between peak serum Na concentration and occurrence of mortality was analyzed using Pearson correlation co-efficient. Analyses were done with SPSS version 16.01. P < 0.05 was considered statistically significant.

**Results**

Among the 670 patients admitted for an acute medical illness under one of the study authors during the study period, HAH developed in 64 (9.5%). The characteristics of the study participants are described in Table 1. The male: Female ratio was 1.8:1. Two hundred and four (30.4%) were in the geriatric age group (>60 years). Pre-existing chronic medical illness was found in 204 (30.4%). Hypertension (35.5%) was the most prevalent chronic illness followed by diabetes mellitus (31.6%) and chronic kidney disease (26.4%). A total 340 (50.7%) had multiple comorbidities. Among the 64 patients with HAH, 44 had no symptoms attributable to raised Na, symptoms could not be analyzed in 14 (22%) who were on mechanical ventilation and 6 (9.4%) had symptoms of hypernatremia (altered cognition with a less likely alternative reason). Biochemical and hematological findings on admission are explained in Table 2.

The median SOFA score on admission was 2/24 (range 0-20) among patients with hypernatremia and 1/24 (range 0-18) for those who did not develop hypernatremia. The median peak SOFA score was 4 among patients with hypernatremia and 8 for those without hypernatremia. Cause of acute illness among the study participants is shown in Table 3. Mechanical ventilation was required for 108 (38 in the hypernatremic group and 70 in the non-hypernatremic group). Clinical categories among 38 mechanically ventilated hypernatremic patients included respiratory sepsis (n = 10), extremity weakness (n = 9), ligation mark over the neck (n = 7), liver flap (n = 4), heart failure (n = 3), airway obstruction (n = 3) and organo-phosphorus poisoning (n = 2), while 70 mechanically ventilated non-hypernatremic patients had respiratory sepsis (n = 30), organophosphorus poisoning (n = 14), heart failure (n = 10), liver flap (n = 6), airway obstruction (n = 4), extremity weakness (n = 3) and ligation mark over neck (n = 3). Mean peak serum Na was 149 meq/l (range 147 - 158 meq/l) in patients with hypernatremia and 138 meq/l (126 - 143 meq/l) in patients without hypernatremia. Mean NaCl intake was 10.5 g (when serum Na was 136 - 139 meq/l), 5.7 g (when serum Na was 140 - 142 meq/l), 2.2 g (when serum Na was 143-145 meq/l) and 0.6 g (patients with serum Na >146 meq/l). Negative fluid balance 24 h before onset of HAH was observed in 84 patients (56 in the non-hypernatremia group and 28 in the hypernatremia group). Patients with a serum Na of 136-139 meq/l (n = 486) received mean free water of 140 ml (range 0-200 ml), those with serum Na 140-142 meq/l (n = 182) received mean free water of 540 ml and participants with serum Na 143 - 145 meq/l (n = 96) received mean free water of 1080 ml. A total 96 of 180 who were admitted with serum Na 140 - 145 meq/l did not have further rise in Na after free water administration. Participants who developed hypernatremia (n = 64) received mean daily free water of 2200 ml (range 1800-4500 ml) during the period of hypernatremia. Free water was administered through a naso-gastric

**Table 1: Baseline characteristics of the study cohort**

| Patient characteristics | All (n=670): Mean±SD or no (%) | Patients without hypernatremia (n=606): Mean±SD or no (%) | Patients with hypernatremia (n=64): Mean±SD or no (%) |
|-------------------------|-------------------------------|---------------------------------------------------------|-----------------------------------------------------|
| Age in years            | 46±22                         | 43±19                                                   | 54±24                                               |
| Sex                     |                               |                                                         |                                                     |
| Male                    | 428 (63.8)                    | 390 (64.35)                                             | 38 (59.3)                                           |
| Female                  | 242 (36.1)                    | 216 (35.64)                                             | 26 (40.6)                                           |
| Co-existing medical illness | 372 (55.5)                 | 330 (54.45)                                             | 42 (65.6)                                           |
| DM                      | 238 (35.5)                    | 204 (33.6)                                              | 34 (53.1)                                           |
| Hypertension            | 98 (14.6)                     | 86 (14.1)                                               | 12 (18.7)                                           |
| Bronchial asthma        | 177 (26.4)                    | 140 (23.1)                                              | 37 (57.8)                                           |
| CAD                     | 64 (9.5)                      | 54 (8.9)                                                | 10 (15.6)                                           |
| COPD                    | 70 (10.4)                     | 62 (10.2)                                               | 8 (12.5)                                            |
| CKD                     | 69 (10.2)                     | 55 (9)                                                  | 14 (21.8)                                           |
| CLD                     | 46 (6.8)                      | 28 (4.6)                                                | 18 (28.1)                                           |
| CVD                     | 26 (3.8)                      | 20 (3.3)                                                | 6 (9.3)                                             |
| Others                  | 180 (26.8)                    | 156 (25.7)                                              | 24 (37.5)                                           |

DM: Diabetes mellitus; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; CLD: Chronic liver disease; CVD: Cerebrovascular disease
Patients without Hypernatremia (n=606): Mean±SD (or) no (%)

Parameter | Patients with hypernatremia (n=64): Mean±SD (or) no (%)
--- | ---
Hb% (g/dl) | 11.2±2.6 12.8±3.6
TC (cells/µl) | 8600±6200 7112±4800
Platelet count (cells/µl) | 2.2±1.2 2.8±1.9
RBS (mg/dl) | 118±38 130±46
Serum creatinine (mg/dl) | 0.94±0.41 1.18±0.36
BUN (mg/dl) | 12±6.3 19±4.6
Serum bilirubin (mg/dl) | 9.2±0.52 1.12±0.68
ALT (IU/l) | 94±46 110±66
AST (IU/l) | 80±38 96±52
SAP (IU/l) | 140±78 160±41
Albumin (g/dl) | 3.2±0.91 3.5±0.73
Globulin (g/dl) | 3.1±1.31 3.3±1.84
Serum Na (meq/l) | 138±3.6 139±4.2
Serum K (meq/l) | 3.9±0.91 4.1±0.72
Serum Cl (meq/l) | 92±14 89±18
Serum HCO3 (meq/l) | 20±5.77 23±3.92
Arterial blood gas
Normal | 360 (59.4) 28 (43.7)
Single acid-base disorder | 144 (23.7) 20 (31.2)
Dual acid-base disorder | 90 (14.8) 10 (15.6)
Triple acid-base disorder | 12 (1.9) 6 (0.9)

TC: Total count; RBS: Random blood sugar; BUN: Blood urea nitrogen; ALT: Alanine transaminase; AST: Aspartate transaminase; SAP: Serum alkaline phosphatase; Hb: Hemoglobin

The median duration of hypernatremia was 3 days (range 1-9 days). Mannitol was administered in 18 hypernatremic patients (6: Stroke; 3: Malignancy; 2: Poisoning; and 7: Hanging) and six non-hypernatremic patients (3: Stroke and 3: Hanging). Frusemide was required by 104 patients (90: Non-hypernatremic group and 14: Hypernatremic group). Sodium bicarbonate was administered in 38 patients (30 in the non-hypernatremia group and eight in the hypernatremia group). Twelve had diarrhea during hospitalization. None had fistula and 12 had intercostal drain for empyema thoracis. Hypernatremia resolved in 52 of 64 participants, but persisted till death in 12 of 64. There was no correlation between peak serum Na value and occurrence of mortality (r = 0.4). Renal concentrating defect, defined as urine osmolality <700 mOsm/kg during hypernatremia, was observed in 60 of the 64 HAH patients.

Multiple logistic regression identified age >60 years (P = 0.02), AKI on admission (P = 0.01), mechanical ventilation (P = 0.01), need for ionotropes (P = 0.03), worsening SOFA score after admission (P < 0.001), enteral tube feeds (P = 0.002), negative fluid balance (P = 0.02) and mannitol use (P < 0.001) as risk factors for HAH [Table 4].

Free water administration of < 500 ml/day was not significantly associated with HAH (P = 0.11). But a free water intake of <1000 ml per day among participants who were mechanically ventilated and were on enteral feeds was significantly associated with HAH (P = 0.01) by univariate analysis.

The mean duration of hospital stay was 9 (non-hypernatremic group) and 11 (hypernatremic group) days. Mortality rate was 19.4% (118 of 606) in non-hypernatremic patients and 34.3% (22 of 64) among hypernatremic patients. The odds for death due to HAH was 1.8 (95% confidence interval: 0.72-2.8).

Discussion

Our study observed a 9.5% prevalence of HAH using a serum Na cut-off ≥146 meq/l, which is less than the 15.3% prevalence observed by an earlier study using a similar cut-off for serum Na. Unlike in earlier studies, which observed patients who were admitted due to medical and surgical illness, participants in the present study were admitted with an acute medical illness, nearly two-third having at least one pre-existing chronic medical illness and over half of them with sepsis as the reason for admission. This fact has important bearing on the clinical application of Table 2: Biochemical and hematological parameters on admission

| Parameter                  | Patients without hypernatremia (n=606): Mean±SD (or) no (%) | Patients with hypernatremia (n=64): Mean±SD (or) no (%) |
|----------------------------|-------------------------------------------------------------|--------------------------------------------------------|
| Hb% (g/dl)                 | 11.2±2.6                                                   | 12.8±3.6                                               |
| TC (cells/µl)              | 8600±6200                                                  | 7112±4800                                              |
| Platelet count (cells/µl)  | 2.2±1.2                                                    | 2.8±1.9                                                |
| RBS (mg/dl)                | 118±38                                                     | 130±46                                                 |
| Serum creatinine (mg/dl)   | 0.94±0.41                                                  | 1.18±0.36                                              |
| BUN (mg/dl)                | 12±6.3                                                     | 19±4.6                                                 |
| Serum bilirubin (mg/dl)    | 9.2±0.52                                                   | 1.12±0.68                                              |
| ALT (IU/l)                 | 94±46                                                      | 110±66                                                 |
| AST (IU/l)                 | 80±38                                                      | 96±52                                                  |
| SAP (IU/l)                 | 140±78                                                     | 160±41                                                 |
| Albumin (g/dl)             | 3.2±0.91                                                   | 3.5±0.73                                                |
| Globulin (g/dl)            | 3.1±1.31                                                   | 3.3±1.84                                                |
| Serum Na (meq/l)           | 138±3.6                                                    | 139±4.2                                                 |
| Serum K (meq/l)            | 3.9±0.91                                                   | 4.1±0.72                                                |
| Serum Cl (meq/l)           | 92±14                                                      | 89±18                                                  |
| Serum HCO₃ (meq/l)         | 20±5.77                                                    | 23±3.92                                                 |

TC: Total count; RBS: Random blood sugar; BUN: Blood urea nitrogen; ALT: Alanine transaminase; AST: Aspartate transaminase; SAP: Serum alkaline phosphatase; Hb: Hemoglobin

Table 3: Cause of acute illness among study participants

| Primary diagnosis | Patients without hypernatremia (n=606) | Patients with hypernatremia (n=64) |
|-------------------|----------------------------------------|-----------------------------------|
| Sepsis            | 341 (56.2)                             | 38 (59.3)                         |
| Stroke            | 33 (5.4)                               | 8 (12.5)                          |
| Acute airway disease | 64 (10.5)                             | 5 (7.8)                           |
| Heart failure     | 81 (13.3)                              | 4 (6.2)                           |
| CAD               | 78 (12.8)                              | 18 (28.1)                         |
| Acute kidney injury | 109 (17.9)                             | 44 (68.7)                         |
| Liver disease     | 26 (4.2)                               | 12 (18.7)                         |
| Hyperglycemic crisis | 38 (6.2)                               | 8 (12.5)                          |
| Poisoning         | 54 (8.9)                               | 6 (9.3)                           |
| Malignancy        | 34 (5.6)                               | 6 (9.3)                           |
| Others            | 86 (14.1)                              | 13 (20.3)                         |

CAD: Coronary artery disease

Discussion

Our study observed a 9.5% prevalence of HAH using a serum Na cut-off ≥146 meq/l, which is less than the 15.3% prevalence observed by an earlier study using a similar cut-off for serum Na. Unlike in earlier studies, which observed patients who were admitted due to medical and surgical illness, participants in the present study were admitted with an acute medical illness, nearly two-third having at least one pre-existing chronic medical illness and over half of them with sepsis as the reason for admission. This fact has important bearing on the clinical application...
of the observations from our study, which should be restricted to HAH among critically ill medical patients and not be extrapolated to other groups especially surgical patients since the pattern of free water loss and hyper-osmolar fluid intake is different in them.[1,8]

Hypernatremia among hospitalized patients is often attributed to decreased administration of electrolyte-free water.[4,6] This is based on well-known physiological principles that explain occurrence of hypernatremia due to lack of access to water.[2] Contrary to these principles we observed that decreased free water administration may not be a major risk factor for HAH for the majority of patients. But at the same time, free water administration <1000 ml/day was associated with HAH among patients on mechanical ventilation and those on enteral feeds. This observation raises the possibility of renal concentrating defects in patients who develop HAH. Individuals with lack of access to water need not necessarily develop hypernatremia if kidneys retain water appropriately (often called appropriate renal response during hypernatremia). Such response could be expected to prevent hypernatremia in this cohort of patients who received inadequate volumes of electrolyte-free water. The fact that 60 of the 64 patients developed HAH points to renal concentrating defect as a major mechanism of the abnormality.

Age >60 years, AKI on admission, mechanical ventilation, worsening SOFA score, need for ionotropes, enteral feeds, negative fluid balance and mannitol use were the risk factors for HAH in our study.

These findings were consistent with earlier studies on HAH, which additionally identified hypokalemia, hypercalcemia, hypoalbuminemia, bicarbonate administration, hyperglycemia and gastrointestinal losses as risk factors for HAH.[1,8,9,10] We did not use renal failure as a separate independent variable since SOFA score was used in the model and the event rate (n = 64) was too low to develop a model addressing individual components of SOFA score. Renal concentrating defect in the setting of hypernatremia has been attributed to diseases associated with central diabetes insipidus, drugs causing nephrogenic diabetes insipidus, hypokalemia, hypercalcemia, loop diuretics and renal dysfunction.[1,4] We preferred to not attribute the renal concentrating defect observed in our patients to specific reasons since it is difficult to establish a causal association.

Hypernatremia (community- or hospital-acquired) is associated with high in-hospital mortality ranging from 30 to 50%,[1,4,8,9,11-13] Mortality among patients who developed HAH was higher (34.3%) compared with those who did not (19.4%) in our study, which is consistent with earlier reports.[1,4,8] However, the study was not designed to identify if HAH is an independent predictor of in-hospital mortality.

The study does have important limitations. First, as mentioned earlier, the observations are restricted to critically ill medical patients. Second, renal concentrating ability was not checked among patients who initially showed a rise in serum Na that responded to additional free water administration. Such data would have shed more light on the renal handling of water among patients who were prevented from developing HAH. This would point to the need for a study that will specifically focus on renal response among all patients showing a rise in serum Na after hospitalization.

The study suggests that administration of electrolyte-free water to prevent HAH should be more meticulously complied with in patients who are elderly, present with AKI, suffer multi-organ dysfunction, require mechanical ventilation, receive enteral feeds and drugs such as mannitol or ionotropes. Although we do not discourage routine free water administration among patients with less severe critical illness and normal serum sodium, the study suggests that these patients may be protected by appropriate renal response.

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How to cite this article: Varun S, Bhaskar E, Abraham G, Arunkumar AS, Renuka MK. Risk factors for hospital-acquired hypernatremia among critically ill medical patients in a setting utilizing a preventive free water protocol: Do we need to do more?. Indian J Crit Care Med 2013;17:28-33.

Source of Support: Nil, Conflict of Interest: None declared.

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