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## Acquired-Hypernatraemia in the Intensive Care Units

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### Abstract:

#### Objectives:

Determine the incidence and predisposing factors of acquired-hypernatraemia in the intensive care units (ICU) and its impact on the outcome.

#### Design:

Observational cross-sectional study with prospective analysis. Setting: Surgical, medical and trauma intensive care units of National Hospital of Sri Lanka.

#### Study Population:

174 consecutive patients were included in this study.

#### Definition:

Hypernatraemia was defined as serum sodium concentration > 145 mmol/l. Results: 74 patients (42.5%) developed hypernatraemia after admission to the intensive care units. Incidence in medical, surgical and trauma ICUs were 47%, 48% and 31% respectively. Significantly lower incidence was reported in patients with trauma compared to the patients from the other two ICUs. High APACHE II (Acute Physiology and Chronic Health Evaluation) score, low GCS (Glasgow Coma Scale), organ dysfunction, transfusion of blood and blood products were associated with an increased incidence of hypernatraemia. Hypernatraemic patients had received significantly greater volume of intravenous fluids exceeding their daily fluid requirement. Compared to normonatraemic patients, hypernatraemic patients demonstrated a longer length of stay (LOS) in the ICU (mean 4.8 days *versus* 11 days,  $p < 0.001$ ) and a higher ICU-mortality rate (15% *versus* 43%,  $p < 0.001$ ).

#### Conclusions:

Severity of the illness, inappropriate intravenous fluid therapy and blood transfusions contribute to the incidence of hypernatraemia in intensive care units. It is associated with increased risk of ICU-mortality and longer length of stay in the ICU.

**Keywords:** Acquired-Hypernatraemia, Hypernatraemia, ICU-length of stay (LOS), ICU-mortality, Intravenous fluid therapy, Normonatraemia, Organ dysfunction.

## INTRODUCTION

Sodium is the most predominant extracellular cation of the body, which plays a pivotal role in regulation of extracellular fluid volume and osmolality. It is maintained at a plasma concentration of 135-145 mmol/l under physiological conditions by a myriad of neuro-humoral mechanisms mediated *via* thirst, arginine-vasopressin, renin-angiotensin-aldosterone axis, sympathetic nervous system and natriuretic peptides [1, 2].

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Hypernatraemia is a frequent complication in critically ill patients, which is associated with increased hospital-mortality [3 - 6]. These patients have a tendency to develop hypernatraemia due to general debility, inadequate access to free water [6] and excessive sodium intake from inappropriate fluid therapy [7]. Several studies have demonstrated ICU-acquired hypernatraemia being independently associated with increased hospital mortality and prolonged length of stay (LOS) in the ICU/hospital [2, 3, 5 - 8]. However, the incidence of acquired-hypernatraemia has not been studied in Sri Lankan intensive care units. Therefore, this study was carried out to determine the incidence of ICU-acquired hypernatraemia, predisposing factors and its impact on the outcome. *i.e.* ICU-mortality and LOS in the ICU.

## MATERIALS AND METHODS

### Study Setting

This prospective, observational cross-sectional study conducted to determine the incidence, predisposing factors and prognostic impact of hypernatraemia acquired by the patients admitted to medical, surgical and trauma ICUs of the National Hospital of Sri Lanka. The ethics review committee of the hospital approved the study.

### Study Population

Data from the patients admitted to the medical, surgical and trauma ICUs were reviewed prospectively from 01.09.2012 to 31.10.2012.

Due to lack of data on the subject within the Sri Lankan context, a study by Darmon *et al.*, which reported an overall 15.3% incidence of ICU-acquired hypernatraemia was employed to calculate the sample size [4]. Applying a confidence level of 95%, a sample size of 174 was calculated. Consecutive patients admitted to the above ICUs, aged 18 years or more, who stayed in the ICU for more than 24 hours, were included in this study. Patients with head injury and post-op neurosurgery were excluded due to their tendency to develop disturbances in sodium homeostasis in consequence to syndromes of Antidiuretic hormone (ADH) imbalance. Further, the patients with hypernatraemia prior to admission were excluded from the study. Assessment of serum electrolytes was carried out in all the patients at the time of admission to the ICU. Those who found hypernatraemic were excluded from the study. Onset of hypernatraemia after the first 24 hours of admission was considered as 'acquired-hypernatraemia'.

### Definition

Hypernatraemia was defined as serum sodium concentration of 145mmol/l or more. It was further classified to mild (145-149mmol/l), moderate (150-155mmol/l) and severe (> 155mmol/l). Acute Physiology and Chronic Health Evaluation (APACHE) II score was used to ascertain the severity of illness on admission. Glasgow Coma Scale (GCS) was used to determine the level of consciousness. Score of less than 15 was considered low GCS. Daily fluid needs were ascertained by the clinicians attending the patients on an individual basis, tailored to their clinical condition. This value was used for comparison with the actual amount received by the patients by the end of the day. The daily sodium requirement was taken as 1-2 mmol/kg/day.

### Data Collection

All study participants were reviewed by the investigators. Data were collected under 6 categories. *i.e.* Demographic data, clinical characteristics on admission, ICU-acquired complications, therapeutic interventions, incidence of hypernatraemia and outcome parameters. Age, gender, admission category (elective and emergency) and time of admission were included as demographic data. Clinical characteristics on admission included the diagnosis, APACHE II score, and presence of chronic medical conditions. ICU-acquired complications comprised of significant bleeding manifestations requiring blood and blood products transfusion, onset of fever (temperature > 38 °C), hypokalaemia (serum potassium concentration < 3.5 mmol/l on more than 2 consecutive occasions), acute kidney injury (rise in serum creatinine more than 26 µmol/l within 48 hours), metabolic acidosis (pH < 7.35), metabolic alkalosis (pH > 7.45), impaired liver function (rise in serum alanine transaminase > 55 U/l, raised total serum bilirubin > 1.5 mg/dl and conjugated bilirubin > 0.4 mg/dl), hypoproteinaemia (total protein < 64 g/l and serum albumin < 35 g/l), low GCS (score less than 15), acute lung injury (PaO<sub>2</sub>/FiO<sub>2</sub> < 300 mmHg) and Adult Respiratory Distress Syndrome (ARDS with PaO<sub>2</sub>/FiO<sub>2</sub> < 200). Ventilatory support, inotropic therapy, feeding (enteral and parenteral), i.v. frusemide therapy, i.v. fluids and administration of blood and blood products were included as therapeutic interventions. ICU length of stay and ICU mortality were the outcome parameters evaluated in this study.

## Statistical Analysis

Data were analysed using SPSS-17 for windows. Discrete variables were expressed as counts and percentages while continuous variables presented as mean and standard deviation. Categorical data were compared using Chi square test. Continuous variables, conforming to a normal distribution were compared using student's *t* test. Those that did not conform to a normal distribution were analysed with Mann-Whitney-U test.

## RESULTS

### Incidence of ICU-Acquired Hypernatraemia

74 of the population (42.5%) developed hypernatraemia following admission. 19, 25, and 30 of them developed mild, moderate and severe hypernatraemia respectively. Incidence was significantly low in trauma ICU compared to the other two units (trauma: 16 vs medical ICU: 27 + surgical ICU: 31;  $p < 0.05$ ).

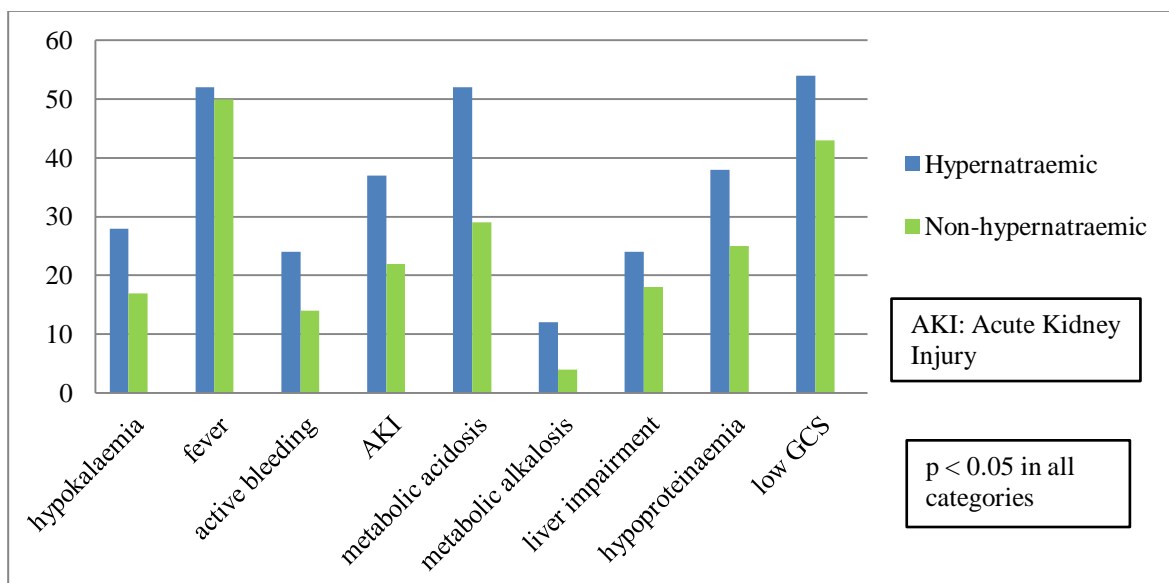
Mean duration of hypernatraemia was 3.5 days. Average duration of ICU-stay, at which it occurred, was 2.6 days. Hypernatraemic patients reported a mean highest serum sodium level of 155 mmol/l (SD: 6.9). Measures were taken to correct hypernatraemia in only 50%. Commonly implemented methods were administration of clear water *via* nasogastric tube, i.v. 5% dextrose and hypotonic saline solutions. Free water deficit was not calculated in any of these patients.

### Characteristics of Patient Population (Table 1)

There was no statistically significant difference in the incidence of ICU-acquired hypernatraemia according to age, gender, body weight, type and time of admission.

### Clinical Characteristics

The incidence was significantly increased in patients with high APACHE II score in first 24 hours. In addition, a number of ICU-acquired complications were found to be associated with a significantly increased incidence of ICU-acquired hypernatraemia. *i.e.* mechanical ventilation, haemodynamic instability requiring inotropic support, other electrolyte disturbances such as hypokalaemia, impaired renal function, fever, low GCS, metabolic acidosis and alkalosis, impaired liver function and hypoproteinaemia (Fig. 1).



**Fig. (1).** Clinical condition after admission and incidence of hypernatraemia.

Moreover, certain therapeutic measures were also associated with an accelerated incidence of ICU-acquired hypernatraemia; *i.e.* transfusion of blood and blood products, i.v. frusemide therapy and i.v. NaHCO<sub>3</sub> therapy (Fig. 2).

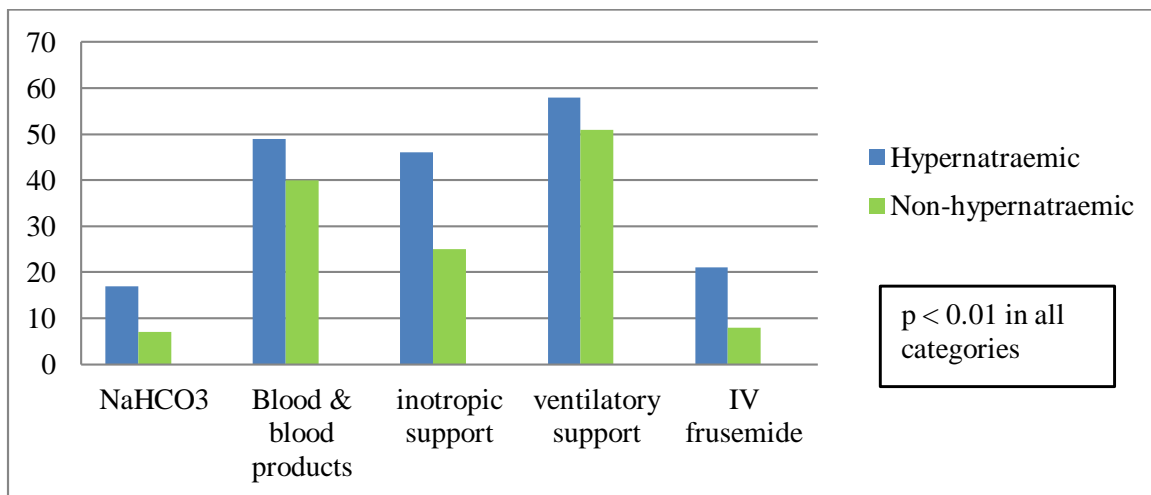


Fig. (2). Therapeutic interventions and incidence of hypernatraemia.

Patients who developed hypernatraemia in the ICU had received significantly higher amounts of intravenous and nasogastric fluids per day. They had also received a higher Na<sup>+</sup> per kg per day intravenously. Interestingly, 140 (80.5%) of the study population had been given intravenous Na<sup>+</sup>, exceeding their daily requirement (1-2 mmol/kg/day) (Table 2). Incidence was not influenced by the presence of chronic medical illness and hyperglycaemia.

Table 1. Comparison of hypernatraemic and non-hypernatraemic patients with reference to demographic variables

Characteristics	Hypernatraemic patients (74)	Non-hypernatraemic patients (100)	Total (174)	p value
Gender (Frequency)				
Male	43 (43%)	56 (57%)	99 (57%)	>0.5
Female	31 (41%)	44 (59%)	75 (43%)	>0.5
Age (Mean years)	51 (SD: 18)	46 (SD: 16)	48 (SD: 16)	0.07
Type of admission (frequency)				
Elective	11 (34%)	21 (66%)	32 (18%)	>0.1
Emergency	63 (44%)	79 (55%)	142 (81%)	
Time of admission (frequency)				
Weekend	11 (37%)	19 (63%)	30 (17%)	>0.5
Night	22 (43%)	30 (58%)	52 (30%)	
Day time	41 (45%)	51 (55%)	92 (53%)	

SD: Standard deviation

## Outcome

Hypernatraemic patients reported a mean length of stay in the ICU of 11 days compared to a mean of 4.8 days in patients without hypernatraemia ( $p < 0.001$ ). ICU mortality in hypernatraemic patients was 43.2% whereas the non-hypernatraemic patients reported a mortality rate of 15% ( $p < 0.001$ ).

## DISCUSSION

Patients managed in the intensive care units tend to develop hypernatraemia more frequently than the general hospital population [7]. Increased insensible loss of water due to mechanical ventilation and fever contributes to hypernatraemia in the ICU. In addition, lack of access to free water as a result of nasogastric feeding, impaired level of consciousness and the underlying illness are some of the factors predisposing to hypernatraemia [7].

This study investigated a heterogeneous group of critically ill patients from medical, surgical and trauma intensive care units. It demonstrated a 42.5% incidence of ICU-acquired hypernatraemia which is higher than the incidence reported in other similar studies. Prevalence of ICU-acquired hypernatraemia varies considerably according to the selected definition. A retrospective study by Waite *et al.*, applying a definition of hypernatraemia of serum [Na<sup>+</sup>] more than 149 mmol/l, reported an incidence of 4.3% [8]. Two other studies by Ariyagari and Lindner *et al.*, using definitions of more than 150 and 149 mmol/l respectively, reported incidences of 7.9% and 9% [4, 6]. However, Sakr and Darmon

*et al.*, used the same definition of hypernatremia as in our study, and demonstrated incidences of 9.5% and 7.88% respectively [2, 3]. Stelfox *et al.*, studied 8142 patients in Canadian surgical and medical ICUs and found a comparatively higher incidence of 26% [6].

Our study compared the patients who developed ICU-acquired hypernatremia with those who did not, in respect to demographic data, complications in the ICU, therapeutic measures and outcome variables. There was no significant difference in the incidence with regard to the age, gender, body weight, presence of chronic medical illnesses, type and time of admission. However, Darmon and Sakr *et al.*, reported a significantly increased incidence of hypernatremia in older patients whereas studies by Lindner and Waite *et al.*, did not show an association with age and incidence of hypernatremia [2, 3, 5, 8]. Waite *et al.*, however discovered a significant association with male gender [8].

Median duration of hypernatremia in our study was 3 days. It was found to be 2 and 1.3 days respectively in studies by Stelfox and Waite *et al.*, [6, 8]. Median time taken to develop hypernatremia following admission to the ICU was 2 days in our study. Other studies reported similar findings [6, 8].

**Table 2. Comparison of hypernatremic and non-hypernatremic patients with regards to disease severity, fluid therapy and me-mechanical ventilation.**

	Hypernatremic patients (74)	Non-hypernatremic patients (100)	Total (174)	p value
Mean APACHE II score	21.5 (SD: 9.57)	13.4 (SD: 8.01)	16.9 (SD:9.54)	0.0001
Mean i.v. fluids/day (ml)	2334 (SD: 1690.5)	1760.6 (SD: 1006)	2004.5(SD: 1366)	0.003
Mean NG fluids/day (ml)*	702.54	442	1056	0.002
Mean daily i.v. Na <sup>+</sup> intake (mmol/kg)	4.94 (SD: 2.97)	3.96 (SD: 2.38)	4.4 (SD: 2.7)	0.01
Mean duration of mechanical ventilation (days)*	8.4	3.4	6	<0.001

\* variables not conforming to normal distribution, hence the SD was not mentioned. SD: standard deviation, NG: naso gastric, APACHE: acute physiology and chronic health evaluation.

Patients with ICU-acquired hypernatremia had a higher APACHE II score compared to patients who did not develop it. Hypernatremia was significantly more prevalent in patients with low GCS score, acute renal and liver impairment, fever, hypoproteinaemia, metabolic acidosis, metabolic alkalosis, hypokalaemia and active bleeding manifestations. All the other studies demonstrated a higher incidence of hypernatremia in patients with higher disease-severity scores [2, 3, 5, 6, 8]. Several studies reported a significantly increased incidence in patients with fever, low GCS, renal, and liver impairment [2, 3, 6 - 8]. Waite *et al.*, reported a significant association of ICU-acquired hypernatremia and upper gastro-intestinal bleeding [8].

Therapeutic interventions such as mechanical ventilation, i.v. frusemide, inotropic support, i.v. NaHCO<sub>3</sub>, blood and blood product transfusion were associated with an increased incidence of ICU-acquired hypernatremia. NaHCO<sub>3</sub> was administered in situations of severe metabolic acidosis secondary to circulatory failure with pH<7.2 despite numerous inotropic therapy. Several studies reported similar associations [3, 6 - 8, 12]. Loop diuretics cause loss of free water in the kidney leading to hypernatremia. Depending on the dose and frequency of administration they could result in significant losses of free water with consequent hypernatremia [9 - 11]. Hypokalaemia is also a well-documented cause of hypernatremia in the critically ill, causing renal concentration defects with resultant loss of free water [7, 9, 11, 12].

Improper intravenous fluid therapy plays a pivotal role in development of hypernatremia as a result of excessive sodium gain [9]. Hypertonic i.v. NaHCO<sub>3</sub> attributes to undue gain of sodium and subsequent development of hypernatremia [9], as demonstrated in our study. Isotonic fluids could also result in hypernatremia [7, 9, 10, 13]. However, their contribution is not widely investigated [9]. Therefore, in this study we analysed the amount and type of intravenous fluids, and the average amount of sodium received intravenously by the patients. 60 out of 174 had received intravenous fluids in excess of their calculated daily fluid requirement. Hypernatremic patients had been given a significantly higher volume of intravenous fluids compared to non-hypernatremic patients. They had received increased amount of NG fluids and higher amount of intravenous sodium per day as well. A vast majority (168 out of 174) had received 0.9% saline. Moreover, the study showed that 81% patients had exceeded the daily sodium requirement through the amount of intravenous fluids they received. Mean sodium intake of the study population was 4.3mmol/kg/d.

Our study showed a higher ICU mortality rate (43.2% vs 15%,  $p<0.001$ ) and a significantly prolonged ICU-LOS in hypernatremic patients. These findings are compatible with various other studies that reported increased ICU and 30-day hospital mortality rates ranging from 32% - 55%. They also reported an association of prolonged ICU-LOS with

ICU-acquired hypernatraemia [2, 3, 5 - 8, 12].

Hypernatraemia is preventable. Meticulous attention should be given for prompt correction while avoiding rapid changes in serum sodium levels. This study revealed that inadequate attention had been given for correction of hypernatraemia. Corrective measures were implemented in only 50% of hypernatraemic patients which included administration of clear water through NG, intravenous hypotonic saline and 5% dextrose. Cause for hypernatraemia was not sought in any of these patients. Accepted methods of correction include; volume resuscitation in case of hypovolaemia, administration of free water for free water deficit and natriuresis with loop diuretics for excess sodium gain [9]. There are no prospective studies on the treatment of hypernatraemia in the ICU. Data are derived primarily from the paediatric population. Accepted rate of correction is less than 0.5 mmol/l/hour, not exceeding a rate of 12 mmol/day [1, 9]. Several formulas have been advocated in current clinical practice to determine the free water deficit, rate of change in serum sodium concentration. *i.e.* Adrogúe-Madias formula [1, 9]. None of these formulae were utilized in the management of these patients.

Our study had several limitations. First, the study did not evaluate the effect of magnitude and duration of hypernatraemia on the outcome. Fluctuations of the sodium concentration have shown to be associated with poor outcome [10]. However, it was not evaluated in this study. Composition of the NG preparations was not taken into consideration. Certain *i.v.* antibiotics are sodium-rich preparations that are shown to contribute to hypernatraemia. Composition of the antibiotic preparations was not evaluated in this study in assessing the sodium intake. Further, the effects of natriuresis were not evaluated.

Assessment of daily sodium balance is an important step in recognizing inadvertent sodium gain which could be helpful in the early detection of hypernatraemia [9]. Renal loss of sodium is rarely ascertained routinely in the ICUs. Further studies are required to evaluate the effectiveness of this method as a predictive tool in the development of ICU-acquired hypernatraemia.

## CONCLUSION

This prospective observational study reveals a relatively higher incidence of hypernatraemia in the critically ill patients compared to literature from the rest of the world. Inappropriate fluid and electrolyte management contribute to the manifestation of ICU-acquired hypernatraemia. It is also a surrogate marker of quality of care. Therefore we recommend attention be paid on this potentially life-threatening complication. Further studies are required to evaluate the treatment of hypernatraemia.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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