

Hyponatremia in critically ill patients

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Abstract

Context: Hyponatremia is a common electrolyte disturbance in critically ill hence understanding its implications is important. **Aims:** This study was carried out to ascertain frequency, predisposing conditions and outcome in critically ill patients with hyponatremia on intensive care unit (ICU) admission. **Settings and Design:** This was an observational, prospective study of a series of ICU patients during a 12-month period. **Materials and Methods:** The patients were divided into two groups: Hyponatremic (serum sodium < 135 mmol/L) and Eunatremic groups (135-145 mmol/L). Clinical examination included volume status and drug history, biochemistries, clinical diagnosis and cause of hyponatremia. **Statistical Analysis Used:** Fisher's exact test, unpaired t-tests Wilcoxon ranksum tests, profile-likelihood method, log-rank test and Kaplan–Meier curves were used. $P < 0.05$ were considered to be statistically significant. **Results:** In the hyponatremic group, the frequency of hyponatremia on ICU admission was 34.3%, most were euvolumic, 58.96%. Females comprised of 36.5%. The mean age was 60.4 ± 17.2 . The Syndrome of inappropriate Antidiuretic Hormone (SIADH) criteria was met in ninety-one patients (36.25%), pneumonia being the leading cause of SIADH. Patients with severe sepsis, elective surgery patients, renal failure and heart failure, cirrhosis of liver and subarachnoid hemorrhage were other more likely etiologic causes ($P < 0.05$). The hyponatremic group spent a longer time in the ICU ($P = 0.02$), had longer mechanical ventilator days ($P < 0.05$) and had an increased mortality rate ($P = 0.01$). **Conclusions:** Hyponatremia present on admission to the ICU is independent risk factors for poor prognosis.

Keywords: Critically ill, epidemiology, hyponatremia

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Introduction

Hyponatremia is a common electrolyte disturbance occurring in critically ill patients.^[1] Symptoms range from nausea and malaise, with mild reduction in the serum sodium, to lethargy, decreased level of consciousness, headache, seizures and coma.

Hyponatremia can be classified on the basis of serum osmolality, volume status and urinary sodium into hypertonic, isotonic and hypotonic types. Hypotonic hyponatremia is further classified into hypervolemic,

euvolemic and hypovolemic as follows:^[2]

- Hypovolemic hyponatremia: Decreased total body sodium and decreased total body water. The sodium deficit exceeding water deficit
- Euvolemic hyponatremia: Normal body sodium with increase in total body water
- Hypervolemic hyponatremia: Increase in total body sodium with greater increase in total body water.

The treatment of hyponatremia depends on the duration of hyponatremia and volume status of the patients. There is serious neurologic sequel if hyponatremia is inappropriately treated. Limited data is available on whether the presence of hyponatremia on intensive care unit (ICU) admission is independently associated with excess mortality. This study was done to ascertain the frequency, aetiology and outcome in critically ill patients admitted to the ICU with hyponatremia.

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Materials and Methods

This was an observational, prospective study of a series of ICU patients during a 12-month period. Hyponatremia was defined as a serum sodium level less than 135 mmol/L. Patients with hyperlipidemias, paraproteinemias (Pseudohyponatremia) and those receiving mannitol, radiographic contrast agents, or having hyperglycemia (translocational hyponatremia) and patients with hypernatremia were excluded. The patients were divided into two groups: Hyponatremic (serum sodium level less than 135 mmol/L) and normal serum sodium (135-145 mmol/L) groups. Hyponatremic patients were further divided into three groups as per volume status as discussed above. History and clinical examination was recorded in all the patients at the time of ICU admission. Detailed drug history was recorded; especially the use of thiazides diuretics and selective serotonin reuptake inhibitors (SSRIs) and clinical evaluation of volume status was done. Parameters for patients including presence of acute renal failure, need for mechanical ventilator and ventilator days, duration of ICU and hospital stay (days) were recorded as observational data and other variables useful to calculate Acute Physiology and Chronic Health Evaluation II (APACHE II) and the sequential organ failure assessment scores were also recorded.^[3]

Laboratory data included values for complete blood count, fasting blood glucose, serum potassium (K), serum urea, serum creatinine, serum uric acid, liver function tests, lipid profile, morning serum cortisol, thyroid function tests. Urine sodium, urine osmolality, serum osmolality, serum sodium were analyzed directly with an iron specific electrode (Cobas b 121 POC system blood gas analyzer and patients were diagnosed to have Syndrome of inappropriate Antidiuretic Hormone (SIADH) if they met its criteria as proposed by Bartter and Schwartz in 1967.^[4]

Statistical analysis

Statistical analysis used: Fisher's exact test, unpaired *t*-tests Wilcoxon ranksum tests, Mantel-cox test, profile-likelihood method, log-rank test, Pearson's test and Kaplan-Meier curves were used. All *P* values were 2-tailed and *P* < 0.05 were considered to be statically significant.

Results

A total of 730 patients were studied, out of which 27 patients were excluded due to presence of hypernatremia (serum sodium > 145 mmol/L), one patient had paraproteinemia and another with

hypertriglyceridemia were excluded. The base line characteristic of study patients is given in Table 1. Of the remaining 699 patients most had normal serum sodium (448, 66.9%). The frequency of hyponatremia on ICU admission was 34.3% of all ICU admissions incidence rate ratio, 1.61; 95% confidence interval [CI], 1.15-2.25, *P* < 0.01. Females comprised of 56.5% of hyponatremic patients and 39.9% of normal serum sodium group. Patients who were taken up for elective surgery were more likely to have hyponatremia than emergency surgery patients (*P* < 0.01). The mean age of patients with hyponatremia was 60.4 ± 17.2. The hyponatremic group had significantly higher APACHE II score when compared to those of the normal serum sodium group (*P* < 0.01). 91 patients (36.25%) of the hyponatremic group met the criteria for a diagnosis of SIADH. The largest group of hyponatremic patients were euvolumic; 148 (58.96%) followed by hypervolumic; 66 (26.29%) and hypovolumic; 37 (14.74%). Etiologic factors causing hyponatremia is given in Figure 1 and Table 2.

SIADH was the most common cause of hyponatremia and pneumonia was the most common cause leading to SIADH. Severe sepsis (sepsis plus at least one acute organ dysfunction secondary to documented or suspected infection)^[5] [Figure 1] and trauma were the

Table 1: Baseline characteristics of the patients*

Variable	Hyponatremia group (n=251)	Normal serum sodium group (n=448)
Age (year)	60.4±17.2	59.9±17.1
Female sex-no./total no. (%)	142 (56.5)	152 (39.9)
IBW [†] (kg)	63.91±15.1	65.21±14.7
Body-mass index [†]	27.9±7.7	28.0±7.2
Interval from ICU admission to serum sodium estimation-h	3.4±1.4	3.4±1.3
Reason for ICU admission-no./total no. (%)		
Operative	12 (4.7)	17 (3.7)
Non-operative	239 (95.21)	431 (96.2)
Location before ICU admission-no./total no. (%)		
Emergency department	67 (26.7)	40 (8.92)
Hospital floor (or ward) admission		
Without previous ICU admission	52 (21)	271 (60.5)
With previous ICU admission	14 (5.5)	9 (2)
Another ICU	10 (3.9)	11 (2.45)
Another hospital	30 (14.7)	13 (16.45)
Operating room		
After emergency surgery	13 (5.17)	30 (6.69) (<i>P</i> =0.24)
After elective surgery	19 (7.56)	12 (2.67) (<i>P</i> <0.1)
APACHE II score	31±8.98	26±7.68 (<i>P</i> <0.01)
Serum sodium level-mmol/L	119±6.6	139±3.5 (<i>P</i> <0.01)

ICU: Intensive care unit; APACHE II: Acute physiology and chronic health evaluation II; IBW: Ideal body weight

next leading causes of hyponatremia [Table 3]. Describes the outcome of hyponatremia of all volume status in critically ill patients. Patients with hyponatremia spent a longer time in the ICU ($P = 0.02$), had longer mechanical ventilator days mean 9.52 ± 5.99 versus 6.48 ± 5.21 ($P = 0.03$) [Table 3] and had an increased

mortality rate [Graph 1] (hazard ratio = 2.23; 95% CI of ratio = 1.323-3.773, $P = 0.01$), than patients in the normal serum sodium group.

Discussion

In our study, the frequency of hyponatremia on ICU admission was 34.3% of all ICU admissions the incidence rate ratio, 1.61; 95% CI, 1.15-2.25, $P < 0.01$ and correlates well with recent studies which have reported hyponatremia to occur in about 30-40% of ICU patients as observed by DeVita *et al.*^[1]

Females comprised of 56.5% of hyponatremic patients and 39.9% of normal serum sodium group. The risk of developing hyponatremia and its complications is higher in women and children compared with men, because of differences in respect of muscle mass and hormonal and anatomical factors.^[6]

Like our study Bennani *et al.* in a study on hyponatremia in ICU found that euvolumic hyponatremia was the most common (50.6%) type of hyponatremia.^[7]

In our study, SIADH is the most common cause of hyponatremia. In a study by Berghmans *et al.* also found that SIADH is the most frequent cause of hyponatremia.^[8] Coussemont *et al.* also found SIADH as a common and potentially lethal complication in critically ill patients.^[9]

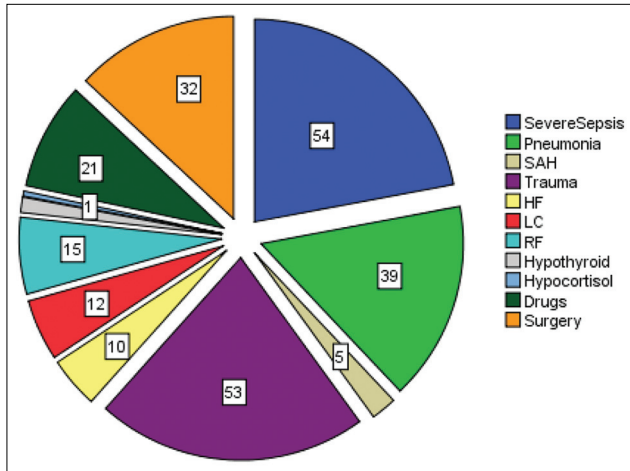
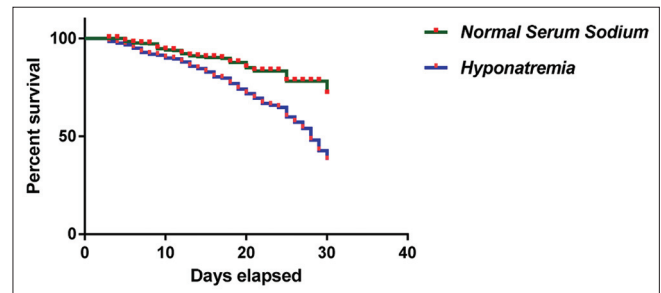


Figure 1: Etiologic factors associated with hyponatremia. SAH = Subarachnoid haemorrhage, HF = Heart failure, LC = Liver cirrhosis, RF = Renal failure

Table 2: Etiologic factors associated with hyponatremia

Disorders	No. of patients (n=251)	Percentage
SIADH* due to	91	36.25
Pneumonia	39	15.53
Drugs including SSRIs†, carbamazepine	15	5.97
Subarachnoid haemorrhage	5	1.99
After elective surgery	19	7.56
After emergency surgery	13	5.17
Severe sepsis	54	21.51
Trauma	53	21.11
Renal failure	15	5.97
Heart failure	13	5.17
Thiazides	12	4.78
Liver cirrhosis	9	3.58
Hypothyroidism	3	1.19
Hypocortisolism	1	0.37

SIADH: Syndrome of inappropriate antidiuretic hormone; SSRIs: Selective serotonin reuptake inhibitors



Graph 1: The time from inclusion to death in the two groups. Comparison of survival curves log-rank (Mantel-Cox) test; $P < 0.0001$

Table 3: Outcomes and adverse events*

Outcome measure	Hyponatremia group (n=251)	Normal group (n=448)	Odds ratio or absolute difference (95% CI)†	Statistical test	P value
Death-no. of patients/total no. (%); all cause 30-day	49/251 (19.5)	74/448 (16.5)	0.4474 (0.3102-0.6454)	Mantel-Haenszel	0.0006
Days in hospital-median (IQR)*	23 (15-23.5)	21 (14-23)	0	Log-rank test	0.15
Mechanical ventilation-no. of patients/total no. (%)	94/251 (37.45)	37/448 (8.25)	0.99 (0.62-1.58)	Pearson's test	<0.01
Days of mechanical ventilation	9.52±5.99	6.48±5.21	0	Wilcoxon rank-sum test	0.03
Renal-replacement therapy-no. of patients/total no. (%)	47/251 (18.7)	28/448 (6.3)	0.33 (0.12-0.87)	Pearson's test	0.03
Days of renal-replacement therapy	0.8±2.3	0.7±2.1	0	Wilcoxon rank-sum test	0.34

IQR: Interquartile range; CI: Confidence interval

In our study severe sepsis is the second most common etiology for hyponatremia. Hannon and Boston observed that hyponatraemia associated with sepsis is known to have an increased morbidity and mortality. The cause of this phenomenon is unknown, but may be related to dilution of the extracellular space with retained exogenous fluid.^[10]

Pneumonia is known to be associated with hyponatremia at the time of admission and it is associated with more severe illness, increased risk of mortality and prolonged hospital stays as reported by Nair *et al.*^[11] In our study, pneumonia at the time of ICU admission, was the most common cause leading to SIADH [Table 2].

In the present study, patients who were taken up for elective surgery were more likely to have hyponatremia than emergency surgery patients. Like our study Leung *et al.* found that perioperative hyponatremia association was particularly marked in patients undergoing nonemergency surgery adjusted odds ratio (aOR), 1.59; 95% CI, 1.50-1.69; $P < 0.001$ and patients with hyponatremia had a higher risk of 30-day mortality and this finding was consistent in all the subgroups. Furthermore, hyponatremia was associated with a greater risk of perioperative major coronary events (1.8% vs. 0.7%; aOR, 1.21; 95% CI, 1.14-1.29), wound infections and pneumonia and prolonged median lengths of stay by approximately 1 day.^[12]

Bissram *et al.* found that symptomatic hyponatraemia was associated with volume depletion (32.6%), congestive heart failure (HF) (26%), SIADH (26%), thiazide diuretic use (26%) and selective serotonin re-uptake inhibitor use (26%). In 21.7% of cases, the cause was multifactorial (congestive HF, SIADH or medication use with volume depletion).^[13]

In our study, hyponatremic patients had longer ICU stay, had longer ventilator days [Table 3] and had an increased mortality [Graph 1]. Shakhe *et al.* also found an increased mortality and ICU length of stay and increased ventilator days among hyponatremic patients admitted to ICU.^[14]

In a large retrospective study in 77 medical, surgical and mixed ICUs in Austria, with a database of 151,486 adults admitted consecutively over a period of 10 years Funk *et al.* demonstrated that all types and grades of dysnatremia were associated with increased mortality.^[15]

However, taking into account all comorbidities and relative severity of illness mortality comparison would

require a large scale regression analysis and subgroup analysis as per volume status for a definitive comment on prognosis.

Conclusion

Hyponatremia is a frequent finding in the critically ill; most of these patients are euvolumic. SIADH is the most common cause of hyponatremia in critically ill. Pneumonia being the leading cause of SIADH. Severe sepsis, trauma, surgery (elective more than emergency), thiazides and other drugs (SSRIs and Carbamazepine), renal failure, HF, liver cirrhosis, subarachnoid haemorrhage, hypothyroidism and hypocortisolism are other etiologic factors for hyponatremia ($P < 0.05$). Hyponatremic patients had longer ICU stay and longer mechanical ventilation days and higher mortality. Patients with hyponatremia had a higher APACHE II score and higher mortality rate than those with normal serum sodium; however, because the former are more severely ill, no causality is apparent or suggested.

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