Sodium Homeostasis and Its Correlation with Mortality in Critically Ill Patients – A Retrospective Study in Northeast India

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ABSTRACT

BACKGROUND
Sodium is the most common electrolyte that gets imbalanced in hospitalised patients. Serum sodium abnormalities carry unacceptably high mortality. Our main objective was to study sodium homeostasis in critically ill patients and to correlate sodium imbalances with mortality in critically ill patients.

METHODS
This was a hospital based retrospective study conducted in Medicine Intensive Care Unit in Assam Medical College and Hospital in Dibrugarh, Assam, India, over a period of one year i.e., from February 2019 to January 2020. Hyponatremia has been defined as sodium level < 135mmol / L and hypernatremia as > 145mmol/L. All patients admitted in MICU of 12 years of age or more have been included in this study. Investigations such as serum creatinine, BUN, sodium, serum osmolality, urine sodium, and urine osmolality as well as neuroimaging were done. A total of 410 patients were studied.

RESULTS
Out of 410 patients, 106 (25.8 %) had hypernatremia, 84 (20.48 %) had hyponatremia and 220 (53.65 %) had normal sodium levels. 225 (54.87 %) patients died. There was a statistically significant correlation between sodium imbalance and death ($p < 0.05$). Mortality in hypernatremia (88.68%) was slightly higher than hyponatremia (79.34 %). It was observed that mortality in hypernatremia (OR = 20.7989, 95% CI: 10.6170 – 40.7454, $p < 0.0001$) and hyponatremia (OR = 10.2015, 95% CI: 5.6651 – 18.3704, $p < 0.0001$) were higher than that of normonatremia. Percentage of death was more in hypernatremia (88.68%) than hyponatremia (79.34%), but the difference was not statistically significant. (OR = 2.0388, 95% CI = 0.9302 to 4.4687, $p = 0.0752$).

CONCLUSIONS
Hyponatremia and hypernatremia are independent mortality factors in critically ill patients. Hypernatremia was more prevalent than hyponatremia in our study and accounted for more number of deaths. Timely and effective correction of sodium levels is important to save a patient's life. Hypernatremia is often iatrogenic. Therefore proper monitoring of sodium is a must.

KEYWORDS
Sodium, Homeostasis, Mortality, Hyponatremia, Hypernatremia

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BACKGROUND

Sodium-related disorders (both hyponatremia and hypernatremia) or dysnatremias are the most commonly encountered electrolyte imbalances and are associated with considerable morbidity and mortality. Sodium is a major extracellular cation in the body and is therefore the most important osmotically active solute other than potassium and chloride. The physiological regulation or homeostasis of sodium level in our body is maintained by basically two mechanisms which involves balancing water intake and water excretion. The former occurs through control of thirst sensation and the latter through control of antidiuretic hormone (ADH) secretion.[1] We require sodium for maintaining water balance, as well as for nerve impulse conduction and muscle contraction. It also helps in maintaining the volume and osmolality of the extracellular fluid.

Hyponatremia is a decline in plasma sodium level that is < 135 mmol / L in blood. Hyponatremia is the most common electrolyte disorder among hospitalized critically ill patients and has been associated with mortality ranging from 5 % to 50 %.[2]

Low plasma sodium in the body depicts a relative water excess. This is mainly associated with renal dysfunction where the kidneys are not able to excrete electrolyte-free water. Removal of excess water by the kidney requires urinary dilution, which is dysfunctional in almost all patients in the ICU: (1) Conditions such as heart failure, sepsis, shock, and multiple organ dysfunction syndrome result in impairment of glomerular filtration and enhancement sodium and water reabsorption at the proximal tubule, thereby diminishing delivery of the filtrate to the diluting segment, i.e., the thick ascending limb of the loop of Henle and the distal convoluted tubule; (2) Reabsorption of sodium and chloride in the diluting segment is reduced in loop diuretics, thiazides, osmotic diuretics, and tubulointerstitial disorders; (3) and nonosmotic stimuli for vasopressin production such as pain, nausea, medications, and hypovolemia lead to increased water reabsorption in the collecting duct. In addition to impaired urinary dilution, hyponatremia in the critical care setting is related to inappropriate administration of hypotonic fluid.

Acute hyponatremia is characterized by onset of symptoms within 48 hours. Symptoms range from nausea and malaise, with mild reduction in the serum sodium, to lethargy, decreased level of consciousness, headache, seizures and coma. It is a true medical emergency and demands prompt treatment. Whether self-induced, drug-related or hospital acquired, acute hyponatremia leads to greater mortality than chronic states.[3] These patients develop neurologic symptoms resulting from cerebral oedema which may include seizures, impaired mental status or coma and death.

However hyponatremia developing over >48 hours is considered to be "chronic." Most patients have chronic hyponatremia where the serum sodium concentration is usually above 120meq/L. Brain adapts itself to hyponatremia by generation of osmolytes. This is a protective mechanism to reduce cerebral edema; it begins on the first day and is complete within several days. Hence in chronic hyponatremia patients may appear asymptomatic. Overt clinical symptoms generally do not occur until plasma sodium level reaches 120 mmol/l. Gastrointestinal tract symptoms like nausea, vomiting, loss of appetite etc. amount to mild hyponatremia. Subtle neurologic abnormalities may be present when the serum sodium is between 120 and 130 meq/L. Hyponatremia in the elderly may manifest with frequent falls and gait disturbances as well as impaired attention. Also it has been associated with fractures and osteoporosis. Infact, the third national health and nutritional examination survey found an Odds ratio of nearly 3 for developing osteoporosis at plasma sodium level of 133 mmol/l compared with normonatremic patients. Hyponatremia was found to be an independent risk factor for fracture of hip. Moreover selective serotonin reuptake inhibitors are found to cause hyponatremia and are associated with falls and fractures in first 2 weeks of therapy. Hyponatremia with congestive heart failure, renal failure and cirrhosis of liver has a worse prognosis and the major concern here is that of encephalopathy. It starts with nonspecific symptoms like headache, lethargy and nausea and later presents with lethargy, depressed reflexes, seizures and coma and ultimately followed by death. Rapid correction of chronic hyponatremia can lead to neurological deficit due to osmotic demyelination and even death. Central pontine myelinosis and extra pontine myelinosis have been grouped under osmotic demyelination syndrome. It usually presents 2-3 days after correction of hyponatremia. Patients present with seizures, parkinsonism, quadriparesis, dysarthria, spastic hypertonia, coma and death. These appear after a brief period of improvement following rapid correction.

According to guidelines, recommended increase in plasma sodium level over 24 hours is less than 10 mmol/l and less than 18 mmol/l over 48 h. Uremia has been found to be protective against osmotic demyelination syndrome as it is associated with more rapid reuptake of osmolytes. Hence it is important to know the cause and treat accordingly. Hyponatremia can be hypovolemic, euvolemic and hypervolemic. Pseudo hyponatremia can occur in hypertriglyceridemia and conditions with raised plasma proteins like multiple myeloma.[4]

Hypernatremia is defined as plasma sodium level more than 145 mmol/L. Hypernatremia is associated with cellular dehydration which then leads to central nervous system damage. It results due to an absolute or relative deficit of free water. Critically ill patients in ICU are unable to control free water intake as a result of sedation, intubation, change in mental status, and fluid restriction for various other reasons. This puts them at a higher risk of developing hypernatremia. In addition, excessive fluid losses from various renal or non-renal sources and treatment with sodium containing fluids are commonly encountered in these patients, predisposing them to hypernatremia.[3]

Hence hypernatremia is the result of hypotonic fluid loss, pure water loss, or hypertonic sodium gain that is sufficient enough to dysregulate the hypothalamic osmoregulatory system. Hypernatremia can be hypovolemic hypernatremia or hypervolemic hypernatremia. Hypovolemic

hypernatraemic patients present with signs of volume depletion and Hypervolemic hypernatremia is caused by the addition of solute in excess of water. Osmotic diuresis could occur due to uncontrolled diabetes. However generation of urea due to high protein diet or protein catabolism can also produce diuresis. It is one of the major causes hypernatremia in hospitalised patients receiving parenteral or enteral nutrition with a high protein load. Apart from these, excessive sweating, emesis, diarrhoea, burns, and tachypnoea are other non-renal causes that can amount to hypernatremia. Major iatrogenic cause is administration of hypertonic and normal saline as well as hypertonic bicarbonate to these critically ill patients.

Treatment of hypernatremia in the ICU or hospital should start with its prevention. Predisposing conditions like uncontrolled diabetes, respiratory failure, polyuria, diarrhoea, fever, inability to take water spontaneously, osmotic diarrhoea etc should be recognised and managed accordingly. Daily monitoring of electrolytes is advised. Therefore, it is important to identify a rising plasma sodium level before severe derangement occurs. Occurrence of iatrogenic hypernatremia indicates poor management of the case. Once recognized, fluid therapy with half normal saline can be modified to prevent progression and correct the adverse effects that have already occurred. The optimal rate of correction of hypernatremia has not been extensively studied, though can be estimated by calculating the water deficit. Hyponatremia is a known risk factor for mortality. However not many studies have been done to relate hypernatremia with mortality. Both the conditions are common and correctable. A broad range of causes should be considered. Understanding the various underlying physiologic principles will help us in establishing the correct diagnosis. A proper knowledge of the condition can optimise the chances of recovery and save many lives. Hence we undertook this study in Assam Medical College and Hospital, Dibrugarh, Assam (India).

Objectives

- To study sodium homeostasis in critically ill patients
- To correlate sodium imbalances with mortality in critically ill patients

METHODS

This is a hospital based retrospective study conducted in the Medicine Intensive Care Unit (MICU) of Assam Medical College and Hospital, Dibrugarh, Assam, India, over a period of one year (February 2019 to January 2020). 140 patients 12 years of age or more admitted in MICU were included in the study.

Inclusion Criteria

1. Age 12 years and above
2. All patients admitted in MICU of AMCH in the mentioned duration of study, i.e., 1-year investigations such as complete blood counts, serum creatinine, BUN, sodium, serum osmolality, urine sodium and urine osmolality, urine routine examination, liver function tests, thyroid function test, cardiac imaging, neuroimaging and other radiological tests were done. All the results were noted and evaluated. Hyponatremia was defined as a serum sodium level less than 135 mmol/L, and hypernatremia was defined as a serum sodium level greater than 145 mmol/L.

Data Extraction

Data has been extracted manually according to checklist from Medical Records Department, Assam Medical College and Hospital as computerised digital records are not available in the hospital.

Statistical Analysis

Data has been presented in frequency and percentage. Odds ratio along with 95% Confidence Interval were calculated and significance was tested by using chi square test. A p value of < 0.05 was considered as significant.
Analysis was done using Medcalc.org calculator.

RESULTS

A total of 410 patients were taken in this study. Out of these 276 (67.31 %) were males and 134 were females (32.68). It was observed that maximum patients (26.09 %) were in the age group of 51 - 60. The investigations showed that 106 (25.8 %) had hypernatremia, 92 (22.43 %) had hyponatremia and 212 (51.70 %) had normal sodium levels.

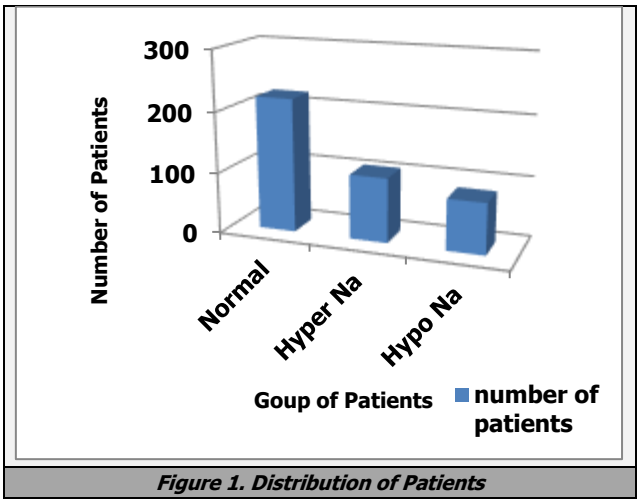

Figure 1. Distribution of Patients

Sodium Abnormality	Number of Deaths	Total Number of Patients	
Hyponatremia	73 (79.34%)	92	p < 0.05
Normonatremia	58 (27.36%)	212	
Hypernatremia	94 (88.68%)	106	
Total	**225**	**410**	

Table 1. Mortality in Critically Ill Patients

Data has been presented in frequency and percentage in table 1. Out of these 410 patients, 225 (54.87 %) patients died. A statistically significant association between sodium

imbalance and death ($p < 0.05$) was found. It was observed that mortality in hypernatremia (OR = 20.7989, 95% CI: 10.6170 – 40.7454, $p < 0.0001$) and hyponatremia (OR = 10.2015, 95% CI: 5.6651 – 18.3704, $p < 0.0001$) were higher than that of normonatremia. Percentage of death was more in hypernatremia (88.68%) than hyponatremia (79.34%), but the difference was not statistically significant. (OR= 2.0388, 95% CI= 0.9302 to 4.4687, p=0.0752).

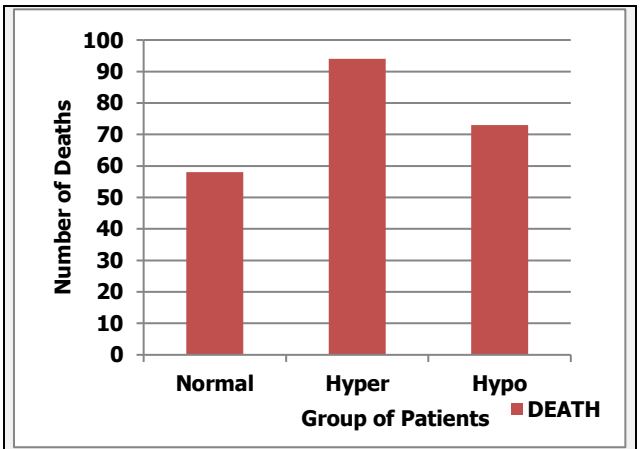

Figure 2. Relation of Sodium Levels with Mortality

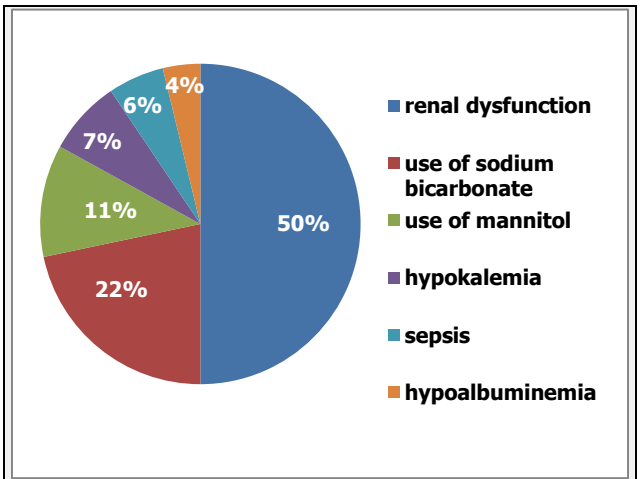

Figure 3. Aetiologic Factors Associated with Hypernatremia

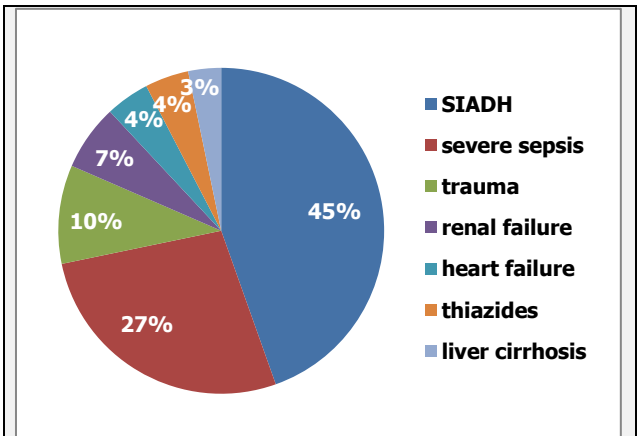

Figure 4. Aetiologic Factors Associated with Hyponatremia

Among the cases of hypernatremia, 53 (50 %) cases had renal dysfunction which was followed by use of sodium bicarbonate (22 %). Use of osmotic diuretics like mannitol was also an important cause of hypernatremia. SIADH was the most important factor in cases of hyponatremia accounting to 45 % of the cases which was followed by severe sepsis (27 %). Trauma, renal failure, heart failure and diuretics were other causes.

DISCUSSION

This study aimed to associate dysnatremia with mortality outcomes in critically ill patients. In this study of sodium homeostasis in critically ill patients, a total of four hundred and ten (410) patients were studied. It was found that maximum patients admitted to MICU during this one year i.e. February 2019 to January 2020 were males (67.31 %). Females comprised of 32.68 %. So there was a sex predilection which was mostly towards males. Most of the patients were in the age group of 51-60 years. This shows that elderly are more prone to develop critical illness than younger age groups.

Among these 410 patients, 51.70 % patients had normal sodium levels. However percentage of patients with hypernatremia (25.8 %) was more than that of hyponatremia (22.43 %). A study by Robert C Hawkins showed that hyponatremia was more common than hypernatremia which did not match with our study.[5] Infact most of the studies done on dysnatremias have shown hyponatremia to be more common than hypernatremia. And so, hypernatremia has not been given much emphasis in the past as it was thought to prevail mainly in the elderly. Moreover out of the 225 dead patients in our study, it was observed that mortality in hypernatremia (88.67 %) was slightly higher than hyponatremia (79.34 %) and was statistically significant. Odds of mortality in hypernatremia was 2 times more than that of hyponatremia. Hence both hypo and hypernatremia were independent risk factors for mortality.

Hypernatremia was found to be an independent mortality factor in the ICU patients. It was attributed to various etiological factors out of which majority of patients had renal dysfunction (50 %). Hypernatremia was associated with underlying diseases (sepsis, trauma), accompanying biochemical disorders (hypokalaemia, hypercalcaemia, renal dysfunction, hyperglycaemia, hypoalbuminaemia), and / or therapy (mannitol, use of sodium bicarbonate-fig 3). These findings were similar to the study of Ewout J. Hoorn et al. Most of the identified risk factors for ICU-acquired hypernatraemia share the ability to promote renal water loss. Hypokalaemia, hypercalcaemia and renal dysfunction can cause a urinary concentrating defect, whereas hyperglycaemia and mannitol can cause osmotic diuresis.[5-11] Vasopressin deficiency in later part of sepsis may lead to further loss of free water. Over correction of hyponatremia and increased production of mineralocorticoids in different stressful conditions of the body could be other factors. Hence dehydration and iatrogenic factors played important role to induce hypernatremia in our patients. Hypernatremia has varied adverse effects on different physiologic functions like

increased peripheral insulin resistance, impairment of hepatic gluconeogenesis as well as lactate clearance and decreased left ventricular contractility.[12] Apart from these, it is associated with various neuromuscular manifestations, such as muscle weakness and cramps. The most severe consequence of hypernatremia is neurologic impairment which may prolong the need for mechanical ventilation and delay weaning. These may explain the association of hypernatremia with increased mortality.

In our study, SIADH is the most common cause of hyponatremia. A study by Berghmans et al. also found that SIADH is the most frequent cause of hyponatremia.[13] (fig-4). Several studies have been done on hyponatremia and our findings correlate with the findings of these studies showing euvolemic hyponatremia to be the commonest. It was followed by sepsis, trauma, renal and heart failure and use of thiazide diuretics. It was mostly associated with underlying chronic disease or comorbidities and hence could be used as a surrogate marker for adverse outcome in those conditions. Finding out the cause and the type of hyponatremia, whether acute or chronic is vital for its correction. Proper correction can save a patient from complications of hyponatremia. Correction rates up to 10 mmol / l per day is acceptable.

This study was carried out to correlate sodium homeostasis with mortality in ICU patients. It has shown that hypernatremia is also an independent mortality factor as hyponatremia. More studies are needed in this aspect at a molecular level to understand the intricacies of this electrolyte and its effects on various organs. Prevention of dysnatremias remains the mainstay for recovery of these patients.

Limitation

It was a retrospective study done in a single centre.

CONCLUSIONS

Hyponatremia and hypernatremia are independent mortality factors in critically ill patients. Several studies are available showing hyponatremia as a prognostic factor for critically ill patients. Gregor Lindner et. al. found in their study that most cases of hypernatremia in the ICU developed after admission, suggesting an iatrogenic component in its evolution. In our study, hypernatremia was more prevalent than hyponatremia. Hypernatremia accounted for more number of deaths than hyponatremia. Timely and effective correction of sodium levels is important to save a patient's life. Hypernatremia is often iatrogenic. Therefore, proper monitoring of sodium is a must. More interventional trials are needed to frame proper guidelines on correction of dysnatremias even though there are some guidelines for hyponatremia. These will help in faster recovery of patients thereby reducing mortality, length of hospital stay as well as hospital costs.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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