Prognostic value of hyponatremia in critically ill children admitted to the pediatric intensive care unit

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ABSTRACT

Background: Hyponatremia is the most common electrolyte disturbance in critically ill children. Although hyponatremia in hospitalized children is associated with adverse outcomes, the risk can be reduced by early diagnosis and intervention. **Objective:** The objective of this study is to identify the outcome of hyponatremia in critically ill children seeking emergency care in the pediatric intensive care unit (PICU). **Methods:** Demographic data, detailed history, systemic examinations, and routine blood and urine investigations were conducted if required for 100 critically ill children aged 1 month–16 years admitted in the PICU. Serum sodium level was classified into the three grades of severity: Mild (131–135 mEq/L), moderate (125–130 mEq/L), and severe (<125 mEq/L). Analysis of urine sodium and urine osmolality was performed. Serum electrolytes and urine spot sodium were measured by ion-sensitive electrode method. **Results:** The overall incidence of hyponatremia was 61% and the survival rate was 78%. Severity of sodium levels was significantly associated with volume status (p<0.0001), ionotropic use (p<0.001), and mortality (p<0.001). Mortality was significantly higher among the hyponatremic children having central nervous system disorders (p=0.04), altered sensorium (p=0.04), ascites (p<0.001), and sepsis (p<0.001). **Conclusion:** Hyponatremia during admission increased the risk of mortality by 5.43 times. Low serum sodium levels at admission also predicted an increased dependency on ionotropic support and mechanical ventilation with dismal patient outcome in terms of survival. However, studies with large sample size and longer duration are required to validate the current findings.

Key words: *Hyponatremia, Inotropes, Mechanical ventilation, Mortality, Normonatremia, Serum sodium*

Electrolyte imbalance in critically ill children admitted to pediatric intensive care unit (PICU) significantly contributes to mortality and morbidity [1,2]. Especially, hospital-acquired hyponatremia is one of the most common electrolyte disorders occurring in approximately 29.7% of the critically ill children [3]. Serum sodium plays a significant role in serum osmolality and tonicity. Although the cases are mild and asymptomatic, hyponatremia is clinically important due to the considerable cause of mortality and morbidity [4].

Contributing factors for hyponatremia are the deficit of sodium or surplus of water, inappropriate release of vasopressin, impaired water excretion, use of hypotonic fluids, redistribution of sodium and water, several drugs, and primary illness [1]. Children with hyponatremia develop symptoms when serum sodium levels fall below 120–125 mEq/L. Headache, coma, seizures, nausea, malaise, lethargy, and unconsciousness are the common symptoms of hyponatremia [5]. Other neurological symptoms include attention deficit, impaired memory or balance, and increased intracranial pressure [6].

Precise information on the pathophysiological implications and outcome of hyponatremia in critically ill children are lacking.

Some researchers view it as less significant, whereas others believe that it is associated with significant mortality and morbidity [7-9]. Hence, the present study was conducted to identify the outcome of hyponatremia in critically ill children seeking emergency care in the PICU.

MATERIALS AND METHODS

This cross-sectional study was conducted between January 2010 and December 2010 at the Department of Pediatrics of a Tertiary Care Hospital. A total of 100 critically ill children admitted to PICU fulfilling the inclusion criteria were the study patients. The sample size was calculated considering average PICU admissions during the past 3 years. Every third child admitted to the PICU was included in the study by applying systematic random sampling technique. The study was approved by the institutional ethical and research committee. An informed written consent was obtained from parents or caregivers of the children.

Children in the study were included based on the Consensus Guidelines for PICUs in India, Indian society of critical care medicine (Pediatric Section), and Indian Academy of Pediatrics

(intensive care chapter) [10]. All children except those with PICU stay of <24 h and who did not fulfill the criteria defining a critically ill child as per the "Consensus Guidelines for PICU of India" were excluded from the study.

Demographic data, detailed history, and systemic examinations of the children were conducted and recorded in a predesigned pro forma. Children who fulfilled the diagnosis of hyponatremia underwent the following investigations: Serum osmolality, urine osmolality, and urine spot sodium. For all critically ill children admitted to the PICU, venous blood of about 3–5ml was collected in a yellow-top vacutainer, and 5–10 ml of urine (spontaneous void or catheter specimen) was collected in a clean sterile bottle. Routine blood and urine investigations such as complete blood count, renal function tests, electrolytes, liver function tests, urine routine, chest radiograph, and other imaging studies were conducted, if required.

The urine sample was sent for the measurement of urine sodium (spot method) and urine osmolality (freezing point depression osmometer). Serum electrolytes and urine spot sodium were measured by ion-sensitive electrode method. Based on the urine osmolality and urine sodium levels and other blood investigation reports, children were classified into hypovolemic, euvolemic, or hypervolemic hyponatremia [8]. Fluid therapy was initiated as per the established practices in PICU, wherein the fluid challenges provided were 0.9% normal saline and maintenance fluids used were dextrose in normal saline or half-normal saline. Ringer's lactate solution was used for the improvement of volume status in cases such as acute gastroenteritis or dengue hemorrhagic fever.

Study Variables

Children were divided into two groups - hyponatremic group and normonatremic group. Parameters such as spectrum of clinical presentation, hydration, hyponatremia, requirement of mechanical ventilatory support, spectrum of diseases, and type of hyponatremia were noted. Other parameters such as length of hospital stay and mortality were also recorded. The outcome recorded was survival/ non-survival in the hyponatremic group as compared to the normonatremic group (serum sodium 136–140 mEq/L). Morbidity was defined as PICU stay of more than 7 days, the requirement of mechanical ventilation during the PICU stay, and the associated comorbid conditions that might have an influence on the adverse outcome of the children in hyponatremic group compared to the children with normal serum sodium levels at admission.

Statistical Analysis

SPSS v20 was used to analyze the data. Receiver operating characteristic (ROC) curve analysis was done to determine the predictive value and optimal cutoff point of serum sodium levels at the time of admission. The student t-test was used to determine statistical difference between improved and expired subjects, based on the parameters measured. Proportions were compared using Chi-square test of significance. Fischer's exact test was used to assess mortality rates in various diagnostic categories. $p \leq 0.05$ was considered statistically significant.

RESULTS

Children with serum sodium levels of <135 mEq/L were considered as hyponatremic based on the ROC curve analysis (Fig. 1). Based on ROC, serum sodium levels ≤135 mEq/l, at the time of admission, maximize the prediction of outcome. At this
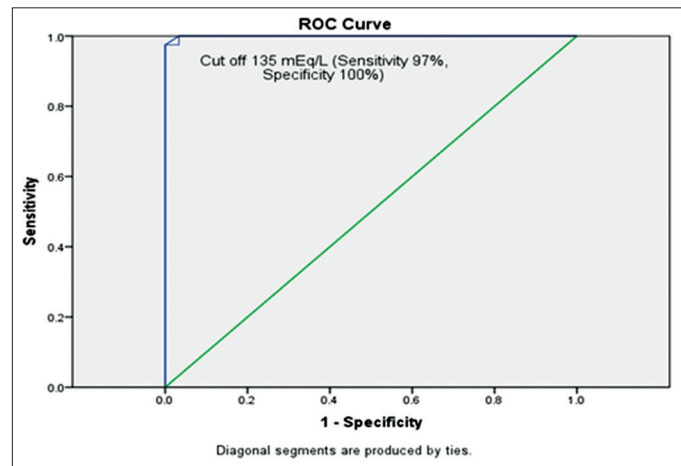

Figure 1: Receiver operating characteristic curve for the diagnosis of hyponatremia at the time of admission

Table 1: Demographic including clinical characteristics of study population

Variables	n (%)
Gender	
Male	70 (70)
Age	
1 month–5 years	59 (59)
6–16 years	41 (41)
Clinical presentation	
Altered sensorium	7 (7)
Convulsion	18 (18)
Shock	34 (34)
Respiratory distress	26 (26)
Pulmonary hemorrhage	1 (1)
Ascites	6 (6)
Bladder tenderness	24 (24)
Sepsis	12 (12)
Congenital heart disease	3 (3)
Serum sodium levels at admission	
Normal	39 (39)
Mild	37 (37)
Moderate	22 (22)
Severe	2 (2)
Incidence of hyponatremia (≤135)	61 (61)
Abnormal volume status at admission (hypovolemia and hypervolemia)	43 (43)
Mechanical ventilation	27 (27)
Requirement of inotropes	43 (43)
Length of hospital stay, <7 days	92 (92)
Improved Outcome	78 (78)

serum sodium level, the sensitivity was 97% and specificity was 100%, with a positive predictive value of 31.1%. The incidence of hyponatremia was observed in 61% of patients, with a mean serum sodium level of 133±4.90 mEq/L, at admission.

Demographic data including clinical characteristics of the study population are given in Table 1. The mean age of the study participants was 5.09±4.63 years. The most common clinical presentation was shock (34%). Most of the children in our study were mild hyponatremic (37 %) and euvolemic (57%), at the time of admission. The overall survival rate was 78% and

length of hospital stay in most of the study population (92%) was <7 days.

Distribution of demographic data including clinical characteristics among normonatremic and hyponatremic children is shown in Table 2. Hyponatremia in boys (67.21%) was higher than in girls (32.79%); however, the difference was statistically insignificant. Altered sensorium, shock, septicemia, respiratory distress, and bleeding manifestations were significantly higher in hyponatremic children, at admission. The frequency of hyponatremia was higher in children with disorders of the

Table 2: Distribution of patients with hyponatremia and normonatremia

Parameters	Normonatremia, n (%)	Hyponatremia, n (%)	p value
Gender, Male	29 (74.36)	41 (67.21)	0.42
Clinical presentation			
Altered sensorium	2 (28.57)	5 (71.43)	<0.001*
Convulsion	9 (50)	9 (50)	>0.05
Shock	7 (20.59)	27 (79.41)	<0.001*
Respiratory distress	9 (34.62)	17 (65.38)	<0.01*
Bladder tenderness	10 (41.67)	14 (58.33)	<0.001*
Sepsis	3 (25)	9 (75)	<0.001*
Comorbid conditions			
CNS disorders	10 (25.64)	12 (19.76)	
Envenomation	1 (2.56)	2 (3.28)	
Hematology	1 (1)	0	
Hepatic	0	3 (4.92)	
Infections	14 (35.90)	14 (22.95)	>0.05
Poisoning	1 (2.56)	4 (6.56)	
Renal	1 (2.56)	3 (4.92)	
Respiratory	6 (15.38)	6 (9.84)	
Surgical	4 (10.26)	10 (16.39)	
Metabolic	0	2 (3.28)	
Ventilation	6 (15.38)	21 (34.43)	<0.001
Hospital stay <7 days	36 (92.31)	56 (91.80)	>0.05
Improved outcome	36 (92.31)	42 (68.85)	<0.001

*Statistically significant. CNS: Central nervous system

Table 3: Association of serum sodium levels at admission with clinical variables

Variables	Serum sodium n (%)			p value
	Normal, n=39	Mild, n=37	Moderate+severe, n=24	
Male	29 (74.36)	23 (62.16)	18 (75)	0.42
Age distribution				
1 month–5 years	24 (61.54)	19 (51.35)	16 (66.66)	0.20
6–16 years	15 (38.46)	24 (48.64)	10 (41.66)	
Referred cases	10 (25.64)	15 (40.54)	4 (16.66)	0.119
Volume status				
Euvolemia	37 (94.87)	13 (35.14)	7 (29.16)	<0.0001*
Hypo+hypervolemia	2 (5.13)	24 (74.05	17 (70.83)	
Ionotropic use	10 (23.26)	17 (39.53)	16 (66.66)	<0.005*
Mechanical ventilation	6 (15.38)	10 (27.03)	11 (45.83)	0.03*
Hospital stay <7 days	36 (92.31)	35 (94.59)	21 (87.5)	0.60
Improved outcome	36 (92.31)	30 (81.08)	12 (50)	<0.001*

*Statistically significant. The number in the parentheses indicates percentage

central nervous system (CNS), infections, respiratory conditions, and surgical patients admitted to our hospital. The requirement of mechanical ventilation (34.43% vs. 15.38%, p<0.001) and improved outcome (68.85 vs. 92.31, p<0.001) was significantly higher in the hyponatremic group compared to normonatremic group. Patients with shock had significantly lower serum sodium levels (130.24±24mEq/L vs. 135.85±4.88 mEq/L) and lower urine sodium levels (19.34±21.03 mEq/L vs. 35.68±23.43 mEq/L) when compared to patients without shock. Mortality was 18.52% among shock patients with low serum sodium levels at admission.

The severity of serum sodium levels was associated significantly with volume status (p<0.0001), referral status (p=0.01), ionotropic use (p<0.001), and outcome (p<0.001) (Table 3).

Mortality was highest among hyponatremic children in the age group of 6–10 years, hypervolemic group, ionotropic group, ventilated children, children with urine sodium <20 mEq/L, and children with <7 days of hospital stay (Table 4).

However, mortality was significantly associated with age (p<0.01), ionotropic requirement (p<0.001), mechanical ventilation

(p=0.007), and volume status (p<0.001) in hyponatremic children. Mortality was significantly higher among the hyponatremic children having CNS disorders compared to normonatremic children with CNS disorders (p=0.04) as shown in Table 5.

Mortality was significantly associated with altered sensorium, ascites, and septicemia among hyponatremic children (Table 6). Binary logistic regression showed that these significant variables were negatively related with mortality (Table 7).

DISCUSSION

The incidence of hyponatremia at admission to our PICU was 61%. However, the range varies between 11 and 50% in different studies based on the methodology used and definition of hyponatremia [11-13]. The higher incidence of hyponatremia encountered in our study is due to the set cutoff value of serum sodium, i.e., <135 mEq/L [11-13].

The incidence of hyponatremia was higher among boys; however, this difference was not significant. The higher male preponderance can be attributed to the prevalent general population behavior, wherein male children are brought more frequently to

Table 4: Association of severity of serum sodium levels with improved outcome among various variables

Variables	Serum sodium levels, n (%)		
	Normal	**Mild**	**Moderate+severe**
Age*			
1 month–5 years	22 (91.67)	18 (94.74)	8 (50)
6–16 years	14 (93.33)	12 (66.67)	4 (50)
Volume status			
Euvolemia	34 (91.89)	12 (92.31)	3 (75)
Hypo/hypervolemia	2 (5.13)	18 (75)	9 (52.94)
Urine sodium <20 mEq/L	-	19 (79.17)	7 (53.84)
Requirement of inotropes*	9 (90)	12 (70.59)	8 (50)
Mechanical ventilation*	3 (50)	4 (40)	2 (18.18)
Hospital stay <7 days	34 (94.44)	29 (82.86)	9 (42.86)

*Statistically significant. The number in the parentheses indicates percentage

Table 5: Incidence of mortality in association with serum sodium levels at admission in various disorders

Diagnosis	Normonatremia, n (%)		Hyponatremia, n (%)		*p* value
	Improved	**Expired**	**Improved**	**Expired**	
Cardiac diseases	0	0	4 (80)	1 (20)	>0.05
CNS disorders	10 (100)	0	7 (58.33)	5 (41.67)	0.04*
Envenomation	1 (100)	0	2 (100)	0	>0.05
Hematology	1 (100)	0	0	0	>0.05
Hepatic diseases	0	0	0	3 (100)	>0.05
Infections	14 (100)	0	10 (71.43)	4 (28.57)	0.98
Other	0	1 (100)	0	0	>0.05
Poisoning	1 (100)	0	4 (100)	0	>0.05
Renal disorders	1 (100)	0	1 (33.33)	2 (66.67)	>0.05
Respiratory diseases	4 (66.67)	2 (33.33)	4 (66.67)	2 (33.33)	1.00
Surgical causes	4 (100)	0	8 (80)	2 (20)	1.00
Systemic disorders	0	0	2 (100)	0	>0.05

*Statistically significant. CNS disorder: Central nervous system disorder

Table 6: Association of clinical presentation with mortality among hyponatremia patients

Clinical presentation	Hyponatremia		p value
	Improved, n (%)	Expired, n (%)	
Altered sensorium	2 (40)	3 (60)	0.04*
Convulsion	5 (55.56)	4 (44.44)	>0.05
Shock	22 (81.48)	5 (18.52)	>0.05
Respiratory distress	9 (52.94)	8 (47.06)	>0.05
Pulmonary Hemorrhage	1 (100)	0	>0.05
Ascites	1 (16.67)	5 (83.33)	<0.001*
Bladder tenderness	6 (42.86)	4 (28.57)	>0.05
Sepsis	3 (33.33)	6 (66.67)	<0.001*
Congenital heart disease	2 (66.67)	1 (33.33)	>0.05

*Statistically significant

Table 7: Relation of clinical presentation with mortality among hyponatremia patients

Clinical presentation	Estimate	p-value
Improved		
Altered sensorium	−2.3514	<0.05
Ascites	−3.5553	<0.05
Sepsis	−2.6391	<0.05

a tertiary care center for emergency care, as compared to female children; however, there is no literature to support of these findings. The mean age of the study population was comparable to other studies in the literature [14,15]. Although most children admitted to PICU were in the age group of 1 month–5 years, the occurrence of hyponatremia was highest in the age group of 6–10 years. However, there is no documentation of such an observation in the literature. In addition, a higher mortality rate was found in children between 6 and 10 years of age with low serum sodium levels at admission. A previous study also suggested that prepubescent children are at an increased risk of developing hyponatremic complications, and many other factors may contribute to this increased risk, especially brain-to-cranial vault ratio [16].

Infectious diseases were the predominant illnesses observed in patients with hyponatremia. With respect to outcome in patients with various disorders, 19 of 61 children expired. Of those 19 children who expired, five had CNS disorder. Similar observations have been reported by Jayakumar *et al.*, wherein 385 of 1076 children had primary CNS disorders, of which 58 were hyponatremic and 10 of them expired [17]. Of the 10 children who died, seven had a CNS infection as the primary pathology.

The frequency of clinical complications in hyponatremic children was higher in this study. Quite similarly, Jenq *et al.* reported a greater frequency of ascites, sepsis, hepatic encephalopathy, and mortality in hyponatremic patients compared to normonatremics [18]. The incidence of hyponatremia increased with disturbances in the volume status of the patients. Likewise, mortality was significantly higher in patients with hypovolemia and hypervolemia compared to those with euvolemia. However, this could not be statistically compared due to the small sample size in this group. Similar results have been reported by

Singhi *et al.*, among hyponatremic patients with respect to the volume status [19]. As per the results of our study in this context, hypervolemia and hypovolemia in hyponatremic children act as independent risk factors for increased mortality.

In this study, mechanical ventilation was significantly higher in hyponatremic patients compared to normonatremics [20]. Furthermore, it was observed that mortality rate was significantly high in hyponatremic patients on ventilation compared to the non-ventilated group. Similar studies conducted by Singhi *et al.* also stated requirement of mechanical ventilation among hyponatremic children compared to normonatremic children; however, this was not statistically significant (58.33% vs. 46.15%, p>0.05) [20].

Most of the children who required inotropes belonged to the hypovolemic-hyponatremic group and had mild hyponatremia. Furthermore, we observed a significant mortality among hyponatremic children who required inotropes compared to those who did not require. Hence, we propose that low serum sodium levels, in conjunction with hypovolemia–hypervolemia, significantly increase the use of inotropes and the subsequent mortality among the children and thus are a marker of serious illness and poor outcome. Similarly, Sachdev *et al.* reported higher use of inotropes in hyponatremic group compared to normonatremic group (12 vs. 4, p=0.04). However, there is a lack of literature to support the mortality findings [21].

No significant association was found between the presence of hyponatremia and prolonged hospitalization. However, many studies reported increased hospital stay as the major risk factor for hyponatremia [19,22]. In this study, 90% of the mortality occurred within 7 days of hospitalization, thereby reducing the overall length of stay of the hyponatremic population. This indicates that the presence of hyponatremia at admission is a marker of serious illness and Herald rapid deterioration in the clinical condition of critically ill children. Hence, we observed an inverse relationship between the hyponatremia at admission and the length of hospital stay.

Mild hyponatremia was the predominant severity of hyponatremia found in our study followed by moderate and severe cases. Similarly, Funk *et al.* reported a 17.7% incidence of hyponatremia in the intensive care unit, with 13.8% classified as

mild, 2.7% as moderate, and 1.2% as severe hyponatremia [23]. In our study, mortality was 5.43 times higher in hyponatremic children as compared to those with normal serum sodium levels at the time of hospitalization. Similarly, in other reports, the risk of mortality is 3 times higher in patients with hyponatremia compared to those with normal serum sodium levels [24,25]. Hence, there was a strong relationship between severity of hyponatremia and mortality. Furthermore, it was noticed that mortality rate increased significantly with the severity of hyponatremia.

CONCLUSION

The presence of hyponatremia at the time of admission among critically ill children increased the risk of mortality by 5.43 times as compared to those with normal serum sodium levels. An adverse outcome in the form of increased mortality and morbidity was associated when hyponatremia, at admission, accompanied with clinical presentation of septicemia, ascites, shock, altered sensorium, and convulsions. Hyponatremia at admission also predicted an increased dependence on ionotropic support and mechanical ventilation with dismal patient outcome in terms of survival. However, studies with a large sample size are required to validate the current findings.

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