ORIGINAL ARTICLE

Prevalence and Outcome of Hyponatremia in Critically Ill Children Admitted to The Pediatric Intensive Care Unit in Tertiary Care Hospital – A Cohort Study

Rishika Jothi Perumalsamy, Sheeja Sugunan, Rekha Krishnan

Abstract

Background: Hyponatremia is the most common electrolyte disturbance observed in hospitalized children with an incidence of 15 - 45%. The proportion is found to be higher in ICU setting. However, presence of hyponatremia worsens the prognosis in ill patients. **Objective:** To find the prevalence and outcome of patients having hyponatremia on morbidity and mortality in PICU. **Methods:** This prospective cohort study conducted at Pediatric Intensive Care Unit (PICU) in a tertiary care teaching hospital in Kerala during 6-month period. **Result:** Out of 410 patients, 253 had hyponatremia on admission with prevalence of 61.71%, 161 had norm natremia and 3 had hypernatremia. Hyponatremia was frequent among patients with pediatric risk of mortality score > 5 %. Severe hyponatremia was also associated with increase in length of PICU stay [p=0.024], increase in requirement of mechanical ventilation andmortality [p = <0.001] in comparison to milder group. Hence hyponatremia severity was independent risk factor of mortality in PICU, but might also confound other risk factors that render the children requiring prolonged hospital stay, mechanical ventilation and mortality. **Conclusion:** Hyponatremia is an independent prognostic factor for mortality: however, the reason for this remains unclear. Hence early recognition of hyponatremia and appropriate intervention will improve the outcome.

Key Words

Hyponatremia, Serum Sodium, Intensive Care Unit

Introduction

Hyponatremia (serum sodium <135 mEq/l)is a commonly encountered electrolyte disturbance in hospitalized pediatric patients with the incidence ranging from 15 to 45 % [1-3] and associated with increase in morbidity and mortality. Previous studies also shows incidence of hyponatremia in adult ICU been 20-30% [4,5]. Clinical manifestation may range from asymptomatic to life-threatening complications but most often present with vague constitutional symptoms. Hyponatremic patients are more likely to require mechanical ventilation, longer stay and mortality when compared with eunatremic patients. Sodium imbalances are influenced by multiple factors like severity of infection, volume status, malnutrition, administration of IV fluids, AKI etc. Serum sodium concentration and serum osmolarity are under the control by homeostatic mechanisms involving stimulation of thirst, secretion of antidiuretic hormone, and renal handling of filtered sodium[6]. Since majority of

Department of Paediatrics, Sree Avittam Thirunal Hospital, Government Medical College, Thiruvananthapuram, Kerala, India.

Correspondence to: Rishika Jothi Perumalsamy, Department of Paediatrics, Sree Avittam Thirunal Hospital, Government Medical College, Thiruvananthapuram, Kerala, India.

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patients are asymptomatic at detection, estimation of serum sodium should be routinely done in all critically ill children. Precise information on the incidence, etiological characteristics, and outcome of hyponatremia in critically ill children is lacking. Hence, aim & objective of the present study was conducted to find the prevalence and outcome of patients having hyponatremia on morbidity and mortality in PICU at tertiary care teaching hospital.

Material and Methods

This prospective observational study was conducted over a six-month period, from August 2019 to January 2020, at the PICU of a tertiary care facility. All children aged from 1 month to 12 years fulfilling the criteria defining a critically child as per the "consensus guidelines for PICU in India" were included in study. Children aged less than 1 month or more than 12 years were excluded.

Sample size was calculated based on the single proportion formula, n= [z1-α/2]2 p q/d2 where proportion of hyponatremia among ICU children was 19% at 95% confidence interval and 20% relative precision.[2] We investigated a total of 410 patients admitted in PICU during the study period after getting written consent from parents or guardian. The study was started after obtaining necessary permission from Institutional Ethical Committee (Serial number: HEC.No.02/45/2019/MCT)

Clinical data including demographic factors ,mode of presentation, clinical features, laboratory investigation as per unit protocols, treatment given and outcome were collected through written proforma. Serum sodium collected only at admission was taken into consideration to find out prevalence. Hyponatremia patients were categorized based on serum sodium levels into mild [131-135], moderate [125-130] and severe [<125]. Morbidity was defined as a PICU stay of more than 7 days, requirement of mechanical ventilation during PICU stay or neurological sequelae. Mortality score PIM3 was calculated by using variables collected from the time of initial patient contact to 1 hour after admission. The outcome recorded was survival or non-survival in the hyponatremia group as compared to the normonatremic group. These demographic and clinical factors were compared between hyponatremia and norm natremia patients, but hypernatremia patients were not compared due to negligible numbers.

Statistical analysis was done using the latest IBM SPSS software version 22. Categorical variables were expressed in frequency and percentages and continuous variables were summarized as mean and standard deviation. Association between outcomes with different parameters was estimated by using chi-square test. P value <0.05 was considered statistically significant. Univariate analysis was performed to calculate crude odds ratio between exposed and unexposed group. Multivariate analysis was done for adjusted odds ratio and independent risk factors were identified.

Results

Out of 410 patients admitted in PICU during the study period, 253 had hyponatremia with high prevalence of 61.7%; 151 had normonatremia; 3 had hypernatremia on admission. In our sample mean sodium level was 133.45 with SD of 6.83. In the present study, out of 253 hyponatremic patients 144 [56.9%] were female 109 [43.1%] male with a male-female ratio of 1:1.3 versus 2:1 among normonatremic patients. Hence females had higher incidence than males [p<0.00001; OR 2.59 [CI 1.709-3.93]]. There was no statistically significant difference in age group affected among hyponatremia and normonatremia cases. [p=0.066; OR 0.728[CI0.485-1.094]]. In patients with PIM3 score > 5 ,81[74.3%] were hyponatremic, while only 28 patients [25.7%] were eunatremic. In our study 42.7% hyponatremic patients vs 29.2% eunatremic patients need ventilation [p=0.006]. 117[46.2%] hyponatremic patients required ICU stay more than 7 days compared to normonatremic patients and showing significant association between hyponatremia and longer ICU stay [p=0.05; OR 1.51[CI 0.998-2.271]. 46[18.2%] hyponatremic patients died during hospital stay, while corresponding figure in normonatremic patients was 5[3.25%] [p=0.00001; OR 6.62[95%CI 2.57-17.1]. Comparison of variables among hyponatremia and eunatremia are shown in Table 1.

Based on severity of Hyponatremia, among 253 cases, 142 [56.13%] had mild, 64 [25.3%] had moderate and 47 [18.58%] had severe hyponatremia. But it was found that younger age group [<12 months] had higher proportion of severe hyponatremia cases [p = 0.014]. Among hyponatremia cases, 29 [61.7%] severe hyponatremia patients had PIM3 >5 vs 34 [23.9%] mild hyponatremia patients [p = 0.001] thus showing significant association between hyponatremia severity and high PIM3 score. The most common underlying disease involved in the study was CNS disease with 78 patients [30.4%], followed by respiratory with 69 [27.3%], cardiovascular 32 [12.6%], renal 17 [6.7%], gastrointestinal 10 [4%]. But severe hyponatremia was more common in patients with respiratory disease [42%] when compared with other diseases. Of hyponatremia cases, 66% severe hyponatremia required ventilation compared to milder group, hence requirement for mechanical ventilation increased significantly with

Table 1: Comparison of Variables Among Hyponatremia and Eunatremia Cases

Category		Hyponatremia [n =253][%]	Eunatremia [n=154][%]	OR	95%CI	P value
Age [months]	0-12	92[36.36]	39[25.32]	0.728	0.485-1.094	0.0665
	12-60	67[26.48]	46[26.62]			
	>60	94[37.15]	69[44.80]			
Gender	Male	109[43.08]	102[66.23]	2.59	1.709-3.93	<0.00001*
	Female	144[56.92]	52[33.77]			
Nutritional status	Normal	200[79.05]	121[78.57]	0.972	0.595-1.586	0.815
	MAM	46[18.18]	27[17.53]			
	SAM	7[2.77]	6[3.9]			
PIM3 score	0-5	172[67.98]	126[81.82]	2.12	1.302-3.45	0.002*
	>5	81[32.02]	28[18.18]			
Mechanical ventilation	Needed	108[42.69]	45[29.22]	1.8	1.177-2.766	0.006*
	Not needed	145[57.31]	109[70.78]			
Duration of ICU stay	1-7 days	136[53.75]	98[63.64]	1.51	0.998-2.271	0.05
	>7 days	117[46.25]	56[36.36]			
Mortality	Survival	207[81.81]	149[96.75]	6.62	2.57-17.1	0.00001*
	Non survival	46[18.18]	5[3.25]			

**- P<0.05 considered statistically significant*
***-MAM – moderate acute malnutrition; SAM – severe acute malnutrition; PIM3 score – pediatric index of mortality 3 score*

hyponatremia severity [p<0.001]. The overall mortality rate was 12%, while in cases with severe hyponatremia the mortality was 46.8% compared to only 7% in mild hyponatremia. Table 2 shows distribution of variables based on severity of hyponatremia.

To analyze the predictive model for PICU mortality, univariate binary regression was done. This model showed moderate and severe hyponatremia associated with mortality (OR =11.62; P =<0.001) and PIM 3 score >5 % (OR =9.645; P-value<0.001) and others are not significantly related to mortality. (Table 3) In logistic regression analysis only PIM3 score were found to be independent risk factor contributing to mortality [shown in Table 4].

Discussion

The research analyzed the effect of hyponatremia on morbidity, mortality, and other factors associated with hyponatremia. The prevalence of hyponatremia in this study was 61.7%. However, in other similar studies, the prevalence of hyponatremia has been reported to be 20-40%[1–3]. On the other hand, Al-Sofyani *et al* study ,the hyponatremic prevalence was comparable with our study, i.e., 67.2%[7]. Prasad *et all* noted a link between the summer season in his study, while other authors also analyzed incidence of hyponatremia with seasonal change[8]. Unfortunately, we could not study the impact of seasonal variation on disturbed serum sodium concentration in this study.

The research demographic and clinical profile in the present study reveals that females have more incidence of hyponatremia than males. Previous studies also showed female sex preponderance similar to our study. The risk of hyponatremia and its complications is found to be higher in women and children when compared to men due to variations in muscle mass, hormonal and anatomical factors[9]. But there was no gender

Table 2: Distribution of Variables Based on Severity of Hyponatremia

Category		Hyponatremia severity								p-Value
		Mild [n=142]		Moderate [n=64]		Severe [n=47]		Total [n=253]		
		N	%	N	%	N	%	n	%	
Gender	Male	62	43.7	23	35.9	24	51.1	109	43.1	0.276
	Female	80	56.3	41	64.1	23	48.9	144	56.9	
Age category [months]	0–12	45	31.7	24	37.5	23	48.9	92	36.36	0.014*
	12–60	33	23.2	24	37.5	10	21.3	67	26.5	
	>60	64	45.1	16	25	14	29.8	94	37.2	
PIM3 score [2 categories]	0–5%	108	76.1	46	21.9	18	38.3	172	68	<0.001*
	>5%	34	23.9	18	28.1	29	61.7	81	32	
Malnutrition	Normal	110	77.5	53	82.8	37	78.7	200	79.1	0.884
	MAM	27	19	10	15.6	9	19.1	46	18.2	
	SAM	5	3.5	1	1.6	1	2.1	7	2.8	
Clinical Presentation	Neurological	38	26.8	32	50	8	17	78	30.8	<0.001*
	Respiratory	33	23.2	16	25	20	42.6	69	27.3	
	Others	31	21.9	12	18.7	4	8.5	47	18.6	
	Cardiovascular	24	15.5	4	6.3	4	8.6	34	12.6	
	Renal	6	4.2	0	0	11	23.4	17	6.7	
	Gastrointestinal	10	7	0	0	0	0	10	4	
Need for Mechanical Ventilation	Yes	45	31.7	32	50	31	66	108	42.7	<0.001*
	No	97	68.3	32	50	16	34	145	57.3	
Duration of ICU stay	0-7 days	83	58.5	25	39.1	28	59.6	136	53.8	0.024*
	>7 days	59	41.5	39	60.9	19	40.4	117	46.2	
Mortality	Non survival	10	7	14	21.9	22	46.8	46	18.2	<0.001*
	Survival	132	93	50	78.1	25	53.2	207	81.8	

**- Chi-square test P<0.05 considered statistically significant*
***-PIM3 score – pediatric index of mortality 3 score*

significance in severity of hyponatremia.

In our study, the highest prevalence was found in the age group of more than 60 months but the difference was not statistically significant; however, children in the age group of 1-12 months had higher incidence of severe hyponatremia [p value <0.005]. The main cause of pediatric hyponatremia is an abundance of free water. This may occur in hypovolemic children with low ECF volume and normovolemic patients with inappropriate increased ADH. A small [1%] increase of osmolality and a high [5-10%] decrease in blood volume are effective stimuli both for ADH secretion & thirst [10,11].

The most common underlying disease involved in the study was CNS disease with 78 patients [30.4%], but severe hyponatremia more common among respiratory patients 69[27.3%]. Previous studies also showed more CNS manifestation among hyponatremic patients[3]. Association of severe hyponatremia in children with respiratory disease has been published in some similar studies[12,13]. Although the underlying mechanism involved in the development of hyponatremia in respiratory infection is unclear, it may probably occur due to SIADH. Fever or dehydration resets the osmostat for ADH or increases the ANP which leads to SIADH[14–16]. Singhi & Dhawan *et al* found that 68 percent of hyponatremia in community-acquired pneumonia had typical characteristics of SIADH[1].

The incidence of severe hyponatremia corresponds with higher pim3 score. Hence patients with PIM3 score >5 along with severe hyponatremia developed unfavorable prognosis. Hyponatremia severity and high pim3 score found to be independent risk factors of mortality in picu. Previously published similar studies also validated the association of PIM3 score with mortality[16].

Table 3: Univariate Model to find Association Between Hyponatremia Severity and other Factors with Mortality

Predictor	Category	Survival	Non survival	OR	95%CI		P-value
Gender	Male	192	21	Ref	-	-	-
	Female	167	30	1.53	0.786	2.976	0.211
Age	0-12	113	18	Ref	-	-	-
[months]	12-60	92	23	0.998	0.477	2.088	0.996
	>60	154	10	0.296	0.124	0.705	0.006*
Hyponatremia	Mild	132	10	Ref	-	-	-
	Moderate	50	14	3.696	1.54	8.86	0.003*
	Severe	25	22	11.62	4.91	27.48	<0.001*
PIM3score	0-5	289	12	Ref	-	-	-
	>5	70	39	9.645	4.629	20.1	<0.001*
Mechanical	Needed	105	51	Ref	-	-	-
Ventilation	Not needed	254	0	0	0	-	0.995
Duration of ICU stay	0-7 days	204	33	Ref	-	-	-
	>7 days	155	18	0.701	0.365	1.35	0.286

**- P<0.05 considered statistically significant*
***- *-PIM3 score – pediatric index of mortality 3 score*

Table 4: Multivariate Logistic Regression Analysis

Predictor	Category	Multivariate model			
		OR	95%CI		p-Value
Hyponatremia	Mild	Ref	-	-	-
	Moderate	3.273	0.95	11.273	0.06
	Severe	2.171	0.559	8.438	0.05
PIM3 score	0-5%	Ref	-	-	-
	>5%	9.418	3.299	26.882	<0.001*
Predicted probability is of membership for Mortality – YES					

**- P<0.05 considered statistically significant*

The present study demonstrated an association between longer ICU stay, increase need for ventilation and increase mortality among hyponatremia cases. Shakhe *et al*. also observed increased mortality and duration of ICU stay and increased days of ventilation among hyponatremic patients admitted to ICU[17]. While hyponatremia has long been recognized as a predictor of severity in critically ill adults[18], the condition in critically ill children is less known. Alternatively, it can simply be a marker of severity [e.g., hyponatremia secondary to elevated antidiuretic hormone secretion, inadequate sodium intake, or iatrogenic hypotonic fluid resuscitation can be correlated with serious illness][10]. So, children with severe hyponatremia need careful monitoring. They have a higher chance of requiring mechanical ventilation, longer hospital stay and increased risk of mortality. In our study, a trend of increase in the length of stay and mortality in picu was seen in correlation with hyponatremic severity. Increased ADH secretion with severe hyponatremia leads to significant impairment of cerebral and vascular function. This can impair the ability of the brain to adapt to hyponatremia. Therefore, in patients with severe hyponatremia, length of stay and need for mechanical ventilation are seen to be increased. A study by Singhi *et al* [19] found 30% longer length of stay in patients with serum sodium below 130 mmol/L. Generally, the severity of the underlying disease is a strong determinant of the duration of stay in PICU. This study reveals that hyponatremia severity is a independent determinant of mortality in PICU. Singhi *et al* study shows a 3-3.5-fold increase in mortality.[19] Overall study suggests that hyponatremic severity is a marker of the severity of the underlying disease as poor prognosis.

Limitations

The present study has several limitations. some confounding factors that would potentially affect outcomes were excluded. We have measured only sodium levels at admission, but cannot able to mention patients developing hyponatremia during hospital stay which also contribute to morbidity & mortality. Effect of fluid administration on hyponatremia cannot able to be addressed.

Conclusion

The conclusion we have drawn from this study is hyponatremia highly prevalent among the pediatric population admitted in intensive care. Those might require a prolonged hospital stay, mechanical ventilation, and increased mortality due to hyponatremia itself or its underlying disease. Since hyponatremia severity is an independent risk factor of mortality in PICU, estimation of the serum electrolytes should be done as a routine in all sick patients

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