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The severity of hyponatremia worsens the outcome in pediatric intensive care patients

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ABSTRACT

Objectives: Hyponatremia is known to increase mortality and morbidity in adult patients. However, the significance of hyponatremia in critically ill pediatric patients is unknown, unlike in adults. We tried to determine the prevalance of hyponatremia in critically ill children and whether the severity of hyponatremia contributes to hospital stay and mortality.

Methods: The results of 190 patients who met the inclusion criteria and were admitted to the pediatric intensive care unit between April 2014 and April 2017 were analyzed.

Results: Eighty-six (45.3%) patients developed hyponatremia at the time of hospitalization, and Hospital−Acquired Hyponatremia (HAH) developed in 46 (24.2%) patients during the hospitalization. Fifty-eight (30.5%) patients were normonatremic. The patients in the HAH group were significantly more septic (p = 0.015). The duration of intensive care hospitalization was significantly longer in the HAH group (p < 0.001) and significantly less in the normonatremic group (p = 0.008). Total mortality was 41% (n = 78). There was no difference between the groups regarding mortality (p = 0.4). However, the degree of hyponatremia was associated with mortality. Mortality was 24.1% in mildly hyponatremic patients, 45.6% in moderate patients, and 58.8% in severe patients (OR: 2.636, 95% CI: 1.189-5.842; OR: 4.490, 95% CI:1.439-14.008, p = 0.01). We discovered that as hyponatremia severity increased, so did the length of stay in the intensive care unit, the need for invasive ventilation, and the need for vasoactive drugs (p = 0.009, p = 0.018, and p = 0.006, respectively).

Conclusions: Unlike adults, the prognostic value of hyponatremia in terms of mortality has not been determined in critically ill children. However, as the severity of hyponatremia increased, it was seen that the length of stay in the intensive care unit and mortality increased.

Keywords: Children, critically ill patients, hospital−acquired hyponatremia, hyponatremia, mortality, severity of hyponatremia

The most common electrolyte imbalance in hospitalized patients is sodium-related electrolyte imbalance [1]. Hospital-acquired hyponatremia was a cause of morbidity and mortality for decades, with the use of hypotonic fluids recommended by Holiday and Segar [1] in 1957 as intravenous maintenance fluid,

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considering the sodium content in breast milk. In accordance with the scientific data of the time, patients were given 77 mEq/L sodium-containing fluid as maintenance fluid during the study [2, 3]. However, we found that hyponatremia is a common problem in hospitalized patients. As a result of dozens of controlled studies, the UK's NICE guideline published in 2017 [4] and the American Academy of Pediatrics Clinical Practice Guidelines published in 2018 recommend isotonic intravenous fluids for maintenance fluid therapy [5].

Hyponatremia is a serum sodium (Na) level below 135 mEq/L. According to the published data, the incidence of hyponatremia in pediatric patients can increase up to 60% at admission to the hospital [6, 7]. The incidence of Hospital−acquired Hyponatremia (HAH) in children is 19.6% [6]. Symptoms of hyponatremia can range from non-specific findings such as restlessness, agitation, headache, and weakness that may be overlooked to serious neurological symptoms such as seizures, confusion, and coma [7]. The symptoms of hyponatremia are determined by the severity and duration of hyponatremia.

In adult patients, hyponatremia is thought to be an independent predictor of mortality [8-10]. In the literature, studies report that hyponatremia increases mortality, but mortality decreases as the severity of hyponatremia worsens [11, 12]. In previous studies, hyponatremia has been evaluated either at hospital admission or in hospital-acquired patient groups. It is a study conducted to eliminate an important information gap in the pediatric patient group. We also aimed to investigate the effects of severity of hyponatremia on the length of stay in the intensive care unit and mortality.

METHODS

The study was initiated after the approval of the Gaziantep University clinical research ethics committee (Decision No: 166). The files of all patients admitted to Gaziantep University Faculty of Medicine's 7-bed tertiary pediatric intensive care unit between April 2014 and April 2017 were reviewed retrospectively. During the current period, 247 patients were hospitalized in our unit, and 34 patients were excluded because they were hypernatremic (Na > 145 mEq/L) at the time of admission. Nine hyperlipidemic and 5 hyperglycemic patients were considered pseudohyponatremic and excluded from the study. The first admission was accepted for patients with recurrent hospitalizations during the study, thus 9 more patients were excluded from the study. The study was initiated with 190 patients. The patients were divided into three groups: Hyponatremia group (patients with hyponatremia at admission hospitalization), HAH group (patients without hyponatremia at admission but with hyponatremia during hospitalization), normonatremia group (patients without hyponatremia during admission and hospitalization).

Plasma sodium levels below 135 mEq/L were defined as hyponatremia. Patients were also grouped according to the severity of hyponatremia as mild (130-134 mEq/L), moderate (125-129 mEq/L) and severe (below 125 mEq/L). The underlying major diagnostic categories were grouped as: Respiratory, cardiac, neurologic, hematological, nephrological, hepatic, trauma, endocrinological and intoxication. As a mortality indicator, the pediatric risk of mortality III (PRISM III) score was used, which was calculated within the first 24 hours of intensive care admission [13].

The medical records of all patients were reviewed, and age, sex, PRISM III scores, cause of ICU hospitalization, need for mechanical ventilation, need for vasoactive medication, presence of sepsis, presence of hyponatremia during the ICU hospitalization, the severity of hyponatremia, and outcome of the patients were noted.

Statistical Analysis

Data were analyzed using SPSS version 22.0. Data were expressed as the means ±standard deviation for normally distributed variables and as the median with interquartile range for non-normally distributed data. Categorical data were expressed as numbers and percentages. Patients with and without hyponatremia during admission to the intensive care unit were compared using the chi-square test for categorical variables. Student’s t−test or ANOVA was used to compare the association between groups for continuous data following normal distribution; otherwise, Mann–Whitney U−test was used. Kruskal-Wallis was used as a non-parametric test in multi-group comparison. $P < 0.05$ was considered statistically significant.

RESULTS

The study included 190 patients who met the inclusion criteria among the 247 patients hospitalized between April 2014 and April 2017. At admission, 86 (45.3%) patients had hyponatremia (serum Na = 130 mEq/L [range: 126-132 130 mEq/L]). When patients with hyponatremia at admission and patients who were normonatremic on admission were compared, no statistically significant difference was found between the two groups in terms of respiratory failure (p = 0.11). The hyponatremic group at admission was associated with significantly less mechanical ventilator need compared to the normonatremic group on admission (OR: 0.377, 95% CI: 0.195-0.731; p = 0.005,) (Table 1). The mean age of the hyponatremic group and the normonatremic group at admission was 46 months (12.7- 120) and 20.5 (8-84) months. Although no statistically significant difference was found in age between the groups, the mean age of the normonatremic group was significantly lower (p = 0.08). The need for mechanical ventilation in normonatremic patients was thought to increase due to a decrease in tolerance to respiratory failure due to anatomical and physiological reasons in the respiratory tract as age decreased. Although there was no statistically significant difference between the groups in terms of PRISM scores, the PRISM values of the hyponatremic group were lower than the normothermic group (p = 0.056) (Table 1).

Acquired hyponatremia developed in 46 (24.2%) patients during the course of ICU hospitalization (HAH group). Patients in the HAH group were significantly more septic (OR: 2.571, 95% CI: 1.185-5.581; p = 0.015,). Hyponatremia never seen in 58 (30.5%) patients, and this patient group was defined as normonatremia. There was no statistical difference between the groups in terms of age and sex. On the other hand, there was no significant difference in the septic picture in the normonatremia and hyponatremia groups (p = 0.25 and p = 0.36, respectively). While the length of ICU stay was significantly longer in the HAH group and significantly shorter in normonatremic patients, no significant difference was observed in hyponatremic patients at admission (p = 0.000, p = 0.008 and p = 0.524, respectively). Total mortality was 41% (n =78). There was no difference between the groups regarding mortality (p = 0.4) (Table 2).

Table 1. Baseline characteristics of the patients at admissions

	Hyponatremia at admission (n = 86)	Normonatremia at admission (n = 104)	*p value*
Age (month)	46 (12.7-120)	20.5 (8-84)	0.08
Gender, n (%)			0.25
Male	45 (52.3)	63 (60.6)	
Female	41 (47.7)	41 (39.4)	
Serum sodium level (mmol/L)	130 (126-132)	140 (136-141)	-
Respiratory failure, n (%)	66 (76.7)	89 (85.6)	0.11
Need for MV, n (%)	54 (62.8)	85 (81.7)	**0.005**
Need for inotropes, n (%)	47 (54.6)	58 (55.8)	0.88
CRRT, n (%)	21 (24.4)	18 (17.3)	0.27
PRISM III	15 (10-20.2)	18 (12-24)	0.056
Length of PICU stay (day)	9 (5-17)	10 (5-17.7)	0.52
Diagnosis of sepsis, n (%)	51 (59.3)	69 (66.3)	0.36 [a]
Mortality, n (%)	33 (38.4)	45 (43.3)	0.49

Data are shown as median with interquartile range (25-75) or number (percent). CRRT = Continuous renal replacement therapy MV = Mechanical ventilation, PICU = pediatric intensive care unit, PRISM = pediatric risk of mortality

Table 2. Comparison of etiological characteristics and outcome in study groups

	Hyponatremia at admission (n = 86)	Hospital-acquired hyponatremia (n = 46)	Normonatremia (n = 58)	*p value*
Age (month)	46 (12.75-120)	18 (6.75-93)	24 (8-87)	0.22
Age group, n (%)				0.19
1-12 month	21 (24.4)	19 (41.3)	24 (41.4)	
12-60 month	27 (31.4)	12 (26.1)	14 (24.1)	
> 60 months	38 (44.2)	15 (32.6)	20 (34.5)	
Gender, n (%)				0.49
Male	45 (52.3)	27 (58.7)	36 (62.1)	
Female	41 (47.7)	19 (41.3)	22 (37.9)	
Respiratory failure, n (%)	66 (76.7)	39 (84.8)	50 (86.2)	0.29
Need for MV, n (%)	54 (62.8)	37 (80.4)	48 (82.7)	**0.013**
Need for vasoactive drugs, n (%)	47 (54.6)	28 (60.9)	30 (51.7)	0.64
Length of hospital stay (day)	9 (5-17)	17 (9-29.2)	8 (4-14.2)	**0.001**
Sepsis n (%)	51 (59.3)	36 (78,3)	33 (56.9)	**0.049**
Major diagnostic category, n (%)				0.17
Respiratory	10 (11.6)	7 (15.2)	7 (12.1)	
Cardiac	15 (17.4)	10 (21.7)	14 (24.1)	
Neurological	14 (16.3)	10 (21.7)	13 (22.4)	
Hematological	19 (22.1)	3 (6.5)	5 (8.6)	
Nephrological	21 (24.4)	9 (19.6)	6 (10.3)	
Hepatic	2 (2.3)	1 (2.2)	1 (1.7)	
Trauma	1 (1.2)	1 (2.2)	3 (5.8)	
Endocrinological	4 (4.6)	3 (6.5)	5 (8.6)	
Intoxication	0 (0.0)	2 (4.3)	4 (6.9)	
Mortality, n (%)	33 (38.4)	17 (36.9)	28 (48.3)	0.4

Data are shown as median with interquartile range (25-75) or number (percent). MV = Mechanical ventilation, PICU = pediatric intensive care unit

However, the severity of hyponatremia was associated with mortality. Mortality was 24.1% in mildly hyponatremic patients, 45.6% in moderate patients, and 58.8% in severe patients (OR: 2.636, 95% CI:1.189-5.842; OR: 4.490, 95% CI:1.439-14.008, $p = 0.01$). We found that as the severity of hyponatremia increased, the length of stay in the intensive care unit, the need for invasive ventilation, and the need for vasoactive medications increased ($p = 0.009$, $p = 0.018$ and $p = 0.006$, respectively) (Table 3).

Sepsis, need for invasive mechanical ventilation, need for vasopressor, and need for CRRT were significantly higher in the deceased group than in the survived group ($p = 0.001$, $p = 0.001$, $p = 0.01$ and $p = 0.029$, respectively). However, there was no difference in terms of mortality between the groups. We found that as the severity of hyponatremia increased, the length of stay in the intensive care unit, the need for invasive ventilation, vasoactive drugs, and even mortality increased.

Table 3. Association of hyponatremia severity with management and outcomes of children in PICU

	Severity of hyponatremia			*p value*
	130-135 (mmol/L) (n = 58)	**125-130 (mmol/L) (n = 57)**	**< 125 (mmol/L) (n = 17)**	
Gender, n (%)				0.11
Male	27 (45.6)	37 (64.9)	8 (47.1)	
Female	31 (53.4)	20 (35.1)	9 (52.9)	
Age category, n (%)				0.81
1-12 months	17 (29.3)	16 (28.1)	7 (23.5)	
12-60 months	18 (31)	16 (28.1)	5 (29.4)	
> 60 months	23 (39.6)	25 (43.8)	5 (29.4)	
Length of PICU stay (day)	8.5 (5-14.7)	14 (7-25.5)	13 (8-32)	**0.009**
Need for MV n (%)	33 (56.9)	43 (75.4)	15 (88.2)	**0.018**
Need for vasoactive drugs, n (%)	24 (41.4)	39 (68.4)	12 (70.6)	**0.006**
Major diagnostic category, n (%)				0.47
Respiratory	8 813.8)	7 (12.3)	2 (11.8)	
Cardiac	7 (12.1)	16 (28.1)	2 (11.8)	
Neurological	11 (19)	9 (15.8)	4 (23.5)	
Hematological	8 (13.8)	12 (21.1)	2 (11.8)	
Nephrological	14 (24.1)	11 (19.3)	5 (29.4)	
Hepatic	2 (3.4)	1 (1.7)	0 (0.0)	
Trauma	2 (3.4)	0 (0.0)	0 (0.0)	
Endocrinological	4 (6.9)	1 (1.7)	2 (11.8)	
Intoxication	2 (3.4)	0 (0.0)	0 (0.0)	
Mortality n (%)	14 (24.1)	26 (45.6)	10 (58.8)	**0.01**

Data are shown as median with interquartile range (25-75) or number (percent). MV = Mechanical ventilation, PICU = pediatric intensive care unit

DISCUSSION

Holliday and Segar [1] proposed a theoretical approach to the maintenance fluid's content and calculation 1957. They stated that hypotonic fluids approaching the sodium and potassium concentrations of breast or cow's milk could meet acutely ill children's water and electrolyte needs. In 1992, a seminal study was published in the British Medical Journal in which 15 of 16 previously healthy pediatric patients were treated with hypotonic fluids post-operatively; 15 died, and the remaining patient suffered permanent brain damage caused by hyponatremia [14]. It was determined that increased ADH due to non-osmotic reasons such as postoperative condition, pain, anxiety, stress, pneumonia, and meningitis in hospitalized patients led to inappropriate ADH release syndrome (SIADH) [15, 16]. Hyponatremia, which developed especially in hospitalized patients, was most often associated with the use of hypotonic fluids [17]. In accordance with the scientific data of the time, patients were given 77 mEq/L sodium-containing fluid as maintenance fluid during the study [2, 3]. Despite this, we discovered that hyponatremia is a common problem in hospitalized patients in our clinic.

Eighty-six of our patients (45.3%) were hyponatremic at admission. Forty-six (24.2%) patients who were not hyponatremic at the beginning became hyponatremic during the course. One of the very few studies conducted on pediatric intensive care patients is the study of Bibi *et al*. [18] in Pakistan. In their study, 865 pediatric intensive care patients were evaluated in a tertiary university hospital; 405 (46.8%) patients had hyponatremia at admission, while hospital-acquired hyponatremia was observed in 240 (27.7%) patients [18]. It is compatible with our cohort. When patients with hyponatremia at admission and patients who were normonatremic on admission were compared, no statistically significant difference was found between the two groups in terms of respiratory failure ($p = 0.11$). In a study comparing hyponatremic and normonatremic patients with bronchiolitis who needed PICU admission, it was found that there was no difference between the two groups in terms of the need for intubation [19]. In our study, interestingly, the hyponatremic group had significantly less need for mechanical ventilators at admission than the normonatremic group.

Unsurprisingly, untreated, rapidly developing severe hyponatremia results in death. The publications about mild-moderate hyponatremia increasing mortality in adult patients, which was previously thought to be almost harmless, are increasing daily [20]. In a seven-year study of over 53,000 hospitalized adult patients, aggravated hyponatremia in the hospital was independently associated with increased mortality [20]. Although there are studies specific to disease subgroups in the adult age group, we realized there were not enough studies on pediatric patients that we treated with hypotonic maintenance fluids for decades. We investigated the impact of hyponatremia on mortality in our clinic, where we could only accept critically ill patients with high PRISM scores due to bed constraints.

Gill *et al*. [21], who evaluated adult patients with serum sodium levels below 125 mEq/L as hyponatremic and compared them with normonatremic patients, found that mortality increased with the deepening of hyponatremia. However, although the threshold value for hyponatremia was accepted as < 125 mEq/L, like Gill *et al*. [21], Chawla *et al*. [11] found the highest mortality rate in patients with sodium values between 120-124 mEq/L, they reported a lower mortality rate of hyponatremia level was less or more severe. They showed it with a parabolic radiograph [11]. They reported that the disparity was due to the nature of the deceased patients' underlying diseases.

Studies on hyponatremia reported that children generally depend on the hypotonic maintenance fluids used. Price *et al*. [22] found the frequency of HAH to be 75% in their study of children with heart failure. All 13 patients with severe hyponatremia either died or required mechanical circulatory support. Wald *et al*. [20] published a study reporting that even mild hyponatremia (1 mEq/L decrease in serum Na) increased in-hospital mortality by 2.3%. They noticed that the relationship between Na level and mortality graph has a U shape, with the lowest death rate in the study being at the 140 mEq/L serum Na level [20]. According to this study, the more severe the hyponatremia, the higher the mortality rate [20]. In this retrospective study on the patients admitted to our pediatric intensive care unit, we discovered that mortality increased as the hyponatremia severity increased. Mortality was 24% in mild hyponatremia, 45.6% in moderate hyponatremia, and 58.8% in severe hyponatremia.

Most studies predict a longer hospital stay in hyponatremic patients [6, 20, 23]. Consistent with the literature, the length of hospital stay of normonatremic patients was significantly lower in our study compared to the other two groups ($p = 0.008$).

In the study conducted on 168 hospitalized severely hyponatremic (< 115 mEq/L) patients, sepsis was highlighted as one of the independent predictors for mortality in multivariate analysis [24]. Shimoyama *et al*. [25] discovered hyponatremia was associated with 28-day mortality in their study of 83 hyponatremic intensive care patients. However, hyponatremia was not associated with mortality in critically ill patients with sepsis [25]. Our study found that the frequency of sepsis increased in the HAH group, the need for longer intensive care unit stay was longer, and we found no increase in mortality. These data are consistent with the existing literature.

Despite many studies emphasizing that hyponatremia is associated with an increased risk of death in adult patients in different disease groups, whether hyponatremia is an indicator of the severity of the underlying comorbidities is still a matter of debate [8, 26, 27]. Luu *et al*. [19] reported that pediatric patients with hyponatremic bronchiolitis admitted to the PICU had worse outcomes and significantly increased mortality compared to normonatremic patients. However, when the study was reviewed in detail, it was seen that 3 (13%) patients who died had comorbidities (metastatic rhabdoid tumor in the first patient, heart failure and severe respiratory failure in the second patient, chronic lung disease and multi-organ failure in the third patient) that caused a high risk of death [19]. In our opinion, comparing mortality with the patient group with only bronchiolitis was not fair. The cause of the significant increase in mortality in the hyponatremia group was thought to be related to the severity of the patients' underlying diseases. In a study by Sachdev *et al*. [6] in India, in which the HAH group and isonatremic control group in PICU were evaluated, no difference was found in terms of mortality in HAH cases, despite the need for prolonged PICU hospitalization and more mechanical ventilation.

Limitations

The limitations of our study are as follows. Our study is a single-centered retrospective study. In accordance with the scientific data of the time, patients were given 77 mEq/L sodium-containing fluid as maintenance fluid during the study. It does not include the patient group in which isotonic fluids are used after the 2018 AAP guidelines recommendations. Furthermore, due to the study's retrospective nature, the amount of fluid intake and sodium content of the patients prior to ICU admission were unknown.

CONCLUSION

In conclusion, the main finding of this study is that mortality increases with the severity of hyponatremia. However, hyponatremia alone is not associated with increased mortality in critically ill pediatric patients. ospital-acquired hyponatremia is associated with a longer intensive care stay and is more common in patients with sepsis. More prospective studies are needed to separate the underlying disease groups one by one and evaluate each factor that may contribute to mortality separately before it can be said that hyponatremia increases mortality in pediatric patients.

Authors' Contribution

Study Conception: MB, AO; Study Design: AO, MB; Supervision: SE; Funding: N/A; Materials: N/A; Data Collection and/or Processing: AO; Statistical Analysis and/or Data Interpretation: AO, SE, MB; Literature Review: SE; Manuscript Preparation: AO and Critical Review: AO, MB, SE.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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