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The Impact of Dysnatremia on Pediatric Intensive Care Mortality

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ABSTRACT

Objective: Fragile nature of the patients in the pediatric intensive care unit (PICU) can lead to severe electrolyte imbalances with life-threatening consequences. Dysnatremia is one of the most common disorders in this setting. This study aimed to investigate the causes, severity and concomitant diseases of dysnatremia in the PICU and factors affecting mortality in these patients.

Material and Methods: This study was carried out between March 2013 and October 2014 in Ankara Children's Hematology Oncology Training and Research Hospital. The patients admitted to PICU between 1 month and 18 years of age were included in the study. Hypernatremic patients were grouped as mild (145>Na≥160 mEq/L) and severe (Na>160 mEq/L); and hyponatremic patients were also grouped as mild (120≤Na <135 mEq/L) and severe (Na<120 mEq/L).

Results: Out of the 101 dysnatremic patients (57 male/ 44 female) with a mean age of 79±71 months, 60% had hypernatremia, 40% had hyponatremia. Eighty-nine (88.1%) of the dysnatremic patients had comorbid chronic diseases, with central nervous system (CNS) disorders as the leading cause. The overall mortality rate of PICU was 17%, and the mortality rate of dysnatremic patients was 53%. The presence of concomitant chronic diseases was associated with increased mortality [OR, 3.84 (CI %95, 0.9-15.1)]. Mortality was more common in patients with severe and uncorrected hypernatremia, respectively (p=0.005, p=0.010).

Conclusion: Dysnatremia is frequent in PICU. The presence of chronic comorbidities, severe and uncorrected dysnatremia increases the risk of mortality in the PICU. Awareness of this risk is important to improve survival in these vulnerable population.

Keywords: Cerebral salt wasting, Diabetes insipidus, Hypernatremia, Hyponatremia

INTRODUCTION

Fluid and electrolyte balance is an important tool for critically ill patients and its management is vital. The fragile nature of most patients in the pediatric intensive care unit (PICU) can lead to severe electrolyte imbalances with life-threatening consequences (1). Dysnatremia is one of the most common disorders in the PICU (2, 3). Abnormal serum sodium concentrations are known to adversely affect physiological function (2, 4, 5). Cells are exposed to hypotonic or hypertonic stress due to disturbances in plasma sodium concentration (4). Therefore, dysnatremia may be associated with adverse outcomes, such as death and permanent neurological damage (2-5). The incidence of dysnatremia on admission to the intensive care unit (ICU) or later during the ICU stay varies among studies. There are publications reporting that one third of critically ill patients are dysnatremic on admission to the ICU and one third develop dysnatremia during their stay in the ICU (6, 7). These sodium disturbances can be caused by an underlying medical condition or concomitant chronic disease as well as end-organ damage, iatrogenic interventions such as fluid and electrolyte management, medications, or the use of critical care technology (8). Multicenter studies focusing specifically on dysnatremia report that it is common in the ICU and is an independent risk factor for ICU mortality (2, 7, 9). This study aimed to investigate the causes,

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Ethics Committee Approval: This study was conducted in accordance with the Helsinki Declaration Principles. Academic approval for the study was from Ankara Pediatric Hematology Oncology Training and Research Hospital (07.05.2013, reference number: 157).

Contribution of the Authors: ***TANER S:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***ÇAKAR N:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar.

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severity and concomitant diseases of dysnatremia in the PICU and factors affecting mortality in these patients.

MATERIALS and METHODS

This study was designed retrospectively in PICU patients of Ankara Children's Haematology Oncology Training and Research Hospital between March 2013 and October 2014. The patients who were hospitalised with a diagnosis of hyponatraemia and hypernatraemia or who developed dysnatraemia during hospitalisation were included in the study. Patients younger than 1 month and older than 18 years of age were excluded from the study. Serum sodium levels of the patients were analysed with ion-selective method using an AU680 Beckman device. Academic approval for the study was from Ankara Pediatric Hematology Oncology Training and Research Hospital (07.05.2013-157). An informed consent was obtained from the participants and their legal guardians included in the study.

Normal sodium levels were considered to be between 135 and 145 mEq/L. Sodium values >145 mEq/L were defined as hypernatremia and sodium values <135 mEq/L were defined as hyponatremia. The classification of the etiological causes of hyponatremia and hypernatremia is shown in Table I. Severe hyponatremia was defined as a serum sodium concentration of less than 120 mEq/L while severe hypernatremia was defined as a serum sodium concentration of more than 160 mEq/L (1, 10). A blood sodium value in the range of 136-145 mEq/L as a result of the treatment given during hospitalisation in the PICU was defined as 'corrected dysnatremia' and these patients were considered as 'treatment responsive'.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics for Wndows, version 21 (IBM Corp., Armonk, N.Y., USA) statistical software. Continuous data were defined as mean and standart deviation in parametric conditions and median (minimum-maximum) in non-parametric conditions. The categorical variables were defined by numbers and percentages. The nominal data were analyzed using the χ^2 test for categorical variables and Fisher's exact test for continuous variables. Logistic regression analysis was used to determine the independent risk factor for mortality. p value ≤0.050 was considered significant.

RESULTS

In this study, out of 1142 patients followed in the PICU during the study period, 101 dysnatremic patients (57 male and 44 female) with a mean age of 79±71 months were included. Sixty percent of the patients had hypernatremia and 40% had hyponatremia. Out of the 40 patients with hyponatremia, 31 had mild hyponatremia and 9 had severe hyponatremia; and out of the 61 patients with hypernatremia, 44 had mild hypernatremia and 17 had severe hypernatremia.

While 87 patients developed dysnatremia during their follow-up in ICU, 14 patients were dysnatremic at the time of admission. Respiratory failure/pneumonia (38.6%) was the most common cause of admission to PICU. Eighty-nine (88.1%) of dysnatremic patients in the study had concomitant chronic diseases. The most common concomitant disease was central nervous system (CNS) disorders such as cranial masses, cranial haemorrhage CNS infections and cerebral palsy. The characteristics of the patients are given in the table (Table II).

Table I: Etiological classification of hypernatremia and hyponatremia

Causes of Hypernatremia	Causes of Hyponatremia	
Excessive sodium intake Inappropriate concentrations of formula Consumption of sodium chloride Salt poisoning (child abuse) Iatrogenic (IV hypertonic saline/sodium chloride) Hyperaldosteronism	Pseudohyponatremia	Euvolemic hyponatremia Syndrome of Inappropriate ADH Desmopressin acetate Glucocorticoid deficiency Hypothyroidism Water poisoning Iatrogenic (excessive hypotonic iv fluid)
Water loss Diabetes insipidus Increased imperceptible losses Insufficient fluid intake	Hyperosmolality (translocational) Hyperglycemia Mannitol	Hypervolemic hyponatremia Congestive heart failure Cirrhosis Nephrotic syndrome Renal failure Capillary leakage due to sepsis Hypoalbuminemia due to gastrointestinal disease
Water and sodium losses Gastrointestinal losses Loss from skin Renal losses	Hypovolemic hyponatremia Extrarenal losses Renal losses Iatrogenic causes (diuretics) Renal diseases causing polyuria Cerebral salt loss Aldosterone deficiency (21 OH deficiency) Pseudo hypoaldosteronism type 1	

Table II: Demographic and clinical characteristics of the patients

Characteristic	Value
Gender (Male/Female)	57/44
Age (months)*	79±71 (1-210)
Hyponatremia/ Hypernatremia	40/61
Time of dysnatremia†	
During follow-up	87 (86.1)
At PICU admission	14 (13.9)
Sodium concentration (mEq/L)*	
Hyponatremia	124±5 (112-129)
Hypernatremia	157±11 (146-200)
PICU follow-up period (days)*	29 ± 35 (1-175)
PICU admission diagnosis†	
Respiratory insufficiency	39 (38.6)
Central nervous system disorders	15 (14.9)
Cardio-pulmonary arrest	12 (11.9)
Sepsis-shock	10 (9.9)
Metabolic diseases	9 (8.9)
Trauma-burn	7 (6.9)
Concomitant disease†	
Yes	89 (88.1)
No	12 (11.9)
Concomitant disease characteristic† (n=89)	
Central nervous system disorders	29 (32.6)
Metabolic	21 (23.6)
Malignity	20 (22.5)
Immune disorders	6 (6.7)
Congenital malformation/syndrome	6 (6.7)
Cardiac	6 (6.7)
Renal	1 (1.1)
Severity of hyponatremia†	
Mild hyponatremia	31 (30.6)
Severe hyponatremia	9 (8.9)
Severity of hypernatremia†	
Mild hypernatremia	44 (43.5)
Severe hypernatremia	17 (16.8)

:** *mean ± SD (min-max),* **†:** *n (%),* ***PICU: *Pediatric Intensive Care Unit*

The most common cause of hypernatremia was iatrogenic diseases in 25 patients (41%). Out of these 25 patients, 10 had intravenous hypertonic fluid intake, 9 had insufficient IV hydration, 5 had diuretic use, and 1 had sodium valproate intoxication. Cerebral salt wasting in 9 patients (23%) was the most common cause of hyponatremia. The causes of cerebral salt wasting were CNS infection in 4 patients (cytomegalovirus, subacute sclerosing panencephalitis, tuberculous meningitis and bacterial meningitis), cranial metastasis in 1 patient, trauma in 2 patients and hypoxia in 2 patients. The cause of iatrogenic hyponatremia was IV hypotonic fluid administration in 3 patients, desmopressin use in 2, diuretic use in 2, insufficient IV hydration in 1. Tubular injury-related loss was found in 6 of the renal-induced hyponatremias, and oliguric state of acute kidney injury was observed in one of these patients. Of the 6 patients with extrarenal-loss caused hyponatremia, 2 had capillary leakage secondary to sepsis, 2 had gastrointestinal losses and 2 had third space losses. The causes of hyponatremia and hypernatremia are shown in Table III.

The number of patients deceased in the PICU during the study was 194, and the overall mortality rate was calculated as 17%. The mortality rate of the dysnatremic patients was 53%. This rate was

Table III: Etiology of hyponatremia and hypernatremia

Hypernatremia* (n=61)	
Iatrogenic	25 (41)
Diabetes insipidus	16 (26)
Renal (acute kidney injury)	13 (21)
Insufficient oral fluid intake	5 (8)
Extrarenal losses	2 (3)
Hyponatremia* (n=40)	
Cerebral salt wasting	9 (23)
Iatrogenic	8 (20)
Syndrome of inappropriate ADH (SIADH)	8 (20)
Renal causes	7 (18)
Extrarenal losses	56 (15)
Translocational hyponatremia (ketoacidosis)	2 (5)

***:** *n(%)*

50% in children with dysnatremia during admission to the PICU and 52.9% in children who developed dysnatremia during follow-up.

There was no statistically significant relationship between mortality and the development time of dysnatremia in dysnatremic patients (p=0.842). The presence of concomitant chronic diseases was associated with increased mortality [OR, 3.84 (CI %95, 0.9-15.1)] in dysnatremic patients.

In order to determine the relationship between the severity of dysnatremia and mortality; hypernatremic patients were grouped as mild (145 <Na ≤160 mEq/L) and severe (Na>160 mEq/L); and hyponatremic patients were similarly grouped as mild (120 ≤ Na <135 mEq/L) and severe (Na<120 mEq/L). Mortality was more common in patients with severe dysnatremia (p=0.005). Eighty-two (79.2%) of 101 dysnatremic patients responded to the treatment. Uncorrected dysnatremia was associated with a higher mortality (p=0.010).

DISCUSSION

In this study, most patients with dysnatremia in the PICU were observed to have concomitant chronic illnesses, and the presence of a concomitant chronic illness was associated with an increased risk of mortality in patients with dysnatremia. In addition, severe dysnatremia and uncorrected sodium disorders were found to be associated with mortality. Dysnatremia is one of the most common electrolyte imbalances in PICU. Dysnatremia may develop on admission to ICU or later during ICU stay (2, 6). The patients developing dysnatremia in the hospital was found to be more than those admitted to the hospital with a diagnosis of dysnatremia (11-15). In our study, likewise, most of the patients developed the disorder during their stay in the PICU. These results show that especially patients being followed in ICU have a risk for developing electrolyte imbalance.

Most patients with hypernatremia monitored in PICU have a related medical condition, commonly a concomitant chronic disease. Hypernatremia was also associated with higher Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) scores, a higher rate of mechanical ventilation and a greater need for inotropic/vasopressor support (14, 16). It is also stated that patients with hyponatremia had more comorbid conditions compared to ones with normonatremia (17). In our study, almost all of the hypernatremic and hyponatremic patients had a comorbid condition or a chronic disease, in line with the literature. Unfortunately, we did not study APACHE II scores.

The most common cause of hypernatremia is iatrogenic illnesses. Iatrogenic causes are commonly inadequate IV hydration and problems reaching the liquid (6, 12). In a 21-year cohort analysis from Netherland, the incidence of hypernatremia was reported to have increased nearly 2-fold. The authors concluded that this increase was also related to such iatrogenic causes as sodium-containing infusions and drug use (18). Karlsson et al. (19) also indicate that a large proportion of documented cases of pediatric dysnatermia are iatrogenic and related to the composition of the intravenous solution (20). In our study, IV use of hypertonic fluids constitutes iatrogenic causes of hypernatremia. The frequent use of IV hypertonic saline therapy as part of the treatment of cerebral edema and frequent follow up of trauma and malignancies in PICU were thought to be the reason for this difference. Previous studies reported that syndrome of inappropriate antidiuretic hormone (SIADH) and iatrogenic causes such as IV administration of hypotonic fluid are the most comman causes of hyponatremia in hospitalized patients (2,21). In their study investigating the etiology of hospital-acquired hyponatremia, Sachdev et al. (22) reported that drug use, iatrogenic fluid intake and post-surgical processes were independent risk factors for the development of hyponatremia. In our study, cerebral salt wasting (22.5%), SIADH (20%) and iatrogenic causes (20%) were the most common causes of hyponatremia.

Dysnatremia in ICU has been shown to have an association with mortality for patients in all ages (23-25). Even daily variability in serum sodium concentration is associated with increased mortality (26). Mai et al. (24) reported that dysnatremia was associated with in-hospital mortality and poor prognosis in children with traumatic brain injury. There are several factors effecting the mortality in dysnatremic patients in PICU (24). Previous studies indicated that dysnatremia at the time of admission or during follow-up were independent risk factors for poor prognosis (2). Stelfox et al. (28) reported that acquired hyponatremia increased the risk of mortality 2-fold (27, 28). There are also studies indicating that acquired hypernatremia is correlated with increased mortality (11, 13, 29, 30). In our study, mortality was more frequent in the presence of dysnatremia. However, there was no significant correlation between the time of development of dysnatremia and mortality. This result may be associated with the small number of patients with dysnatremia at admission to the hospital in this study. Malignancies, trauma, or critical postoperative follow-ups are other important factors affecting high mortality in PICU. The relationship between mortality and dysnatremia can not be evaluated independently due to concomitant diseases occuring during follow-up (15). Dysnatremia has also been shown to cause an increased risk of mortality in the presence of organ dysfunction and concomitant chronic disease (31). Similarly, our study revealed that dysnatremic patients with chronic diseases have been associated with an increased risk of mortality.

Severe dysnatremia is associated with increased mortality. However, survival is closely related to the underlying diseases (15, 18, 32, 33). Severe dysnatremia had an increased mortality rates compared to mild dysnatremia in our study. However, most of the patients had comorbid chronic diseases, making it difficult to attribute mortality to sodium disorders alone. Uncorrected and prolonged hypernatremia is an important factor increasing the mortality (11, 34). Furthermore, the resolution of hyponatremia during hospitalization reduces the increased mortality risk conferred by hyponatremia (5, 14, 17, 35). Thongprayoon et al. (11) also reported that hypernatremia that could not be corrected within 3 days was associated with increased mortality. Similar findings have been shown in other studies (12, 15). In our study, similar to several others, sodium disorder was associated with increased mortality.

Dysnatremia is frequent in PICU. In this study, the most common cause of hypernatremia and hyponatremia was found to be iatrogenic and cerebral salt wasting, respectively. The majority of patients with dysnatremia had a concomitant chronic disease. The presence of concomitant chronic diseases is associated with increased mortality risk in the patients with dysnatremia. Moreover, severe dysnatremia and uncorrected sodium disorders are found to be associated with mortality. In conclusion, dysnatremia increases the risk of mortality in PICU. Therefore, the awareness of this risk is important for the survival of this vulnerable population.

STRENGTHS and LIMITATIONS

This study significantly contributes to the literature with the high number of patients reporting dysnatremia in PICU from a single center. This is one of the strengths of our study. The retrospective design and the unevaluated duration of dysnatremia are the limitations of our study. Another limitation of our study was that the APACHE-II scores assessing risk factors for mortality were not included.

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