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Hyponatremia and Its Effects on Prognosis in A Tertiary Pediatric Intensive Care Unit

Hiponatremi ve Etkilerinin Üçüncü Basamak Pediatri Yoğun Bakım Hastalarında Değerlendirilmesi

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ABSTRACT

Objective: Hyponatremia is accepted as an independent risk factor in pediatric intensive care units. Many comorbidities such as infectious diseases, central nervous system problems and incorrect replacement solutions are blamed in the pathogenesis of hyponatremia. In this study, we aimed to investigate the etiology and prognosis of hyponatremia in a tertiary pediatric intensive care unit.

Material and Methods: We retrospectively analyzed 342 pediatric patients hospitalized in the pediatric intensive care unit of Kayseri City Hospital. Patients with a serum sodium level below 135 mEq/L were considered hyponatremia. Critical hyponatremia was defined as serum sodium less than 125 mEq/L. Data on length of hospital stay, mortality and comorbidities were analyzed.

Results: The data of 342 pediatric patients were evaluated. The male/female ratio was 192/150 (56.1% vs. 43.9%). The mean age of the patients was 41.78 months (±57.7) (min-max 1-212). Twenty-five patients had serum sodium below 125 mEq/L, which could be defined as critical hyponatremia. The mean sodium was 131 (±3.3) mEq/L (min-max: 109-134). The levels of serum creatinine significantly differs before and after treatment ($p<0.001$). The mean resolution time of hyponatremia was 2.1 days (±1.29) (min-max: 1-12) Serum sodium was 125 mEq/L and below in a total of 23 patients. The mortality rate was 23% in all patients at the end of their follow-up.

Conclusion: Hyponatremia is a common problem in pediatric intensive care unit. Especially severe hyponatremia can be related with increased mortality. Close monitoring of sodium is needed in especially trauma patients and central pathologies as well as bronchopneumonia patients.

Key Words: Child, Hyponatremia, Sodium

ÖZ

Amaç: Çocuk yoğun bakım ünitelerinde hiponatremi bağımsız bir risk faktörü olarak kabul edilmektedir. Hiponatreminin patogenezinde enfeksiyon hastalıkları, merkezi sinir sistemi sorunları ve yanlış replasman sıvılarının kullanımı gibi birçok faktör bulunmaktadır. Bu çalışmada üçüncü basamak bir pediatrik yoğun bakım ünitesinde hiponatreminin etiyolojisini ve prognozunu araştırmayı amaçladık.

Gereç ve Yöntemler: Kayseri Şehir Hastanesi 3. Basamak Çocuk Yoğun Bakım Ünitesi'nde yatan 342 çocuk hastayı retrospektif olarak inceledik. Serum sodyum düzeyi 135 mEq/L'nin altında olan hastalar hiponatremi olarak kabul edildi.

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Kritik hiponatremi, serum sodyumunun 125 mEq/L'den az olması olarak tanımlandı. Hastanede kalış süresi, mortalite ve komorbiditelere ilişkin veriler analiz edildi.

Bulgular: 342 pediatrik hastanın verileri değerlendirildi. Erkek/kadın oranı 192/150 (%56.1'e karşı %43.9)'du. Hastaların yaş ortalaması 41.78 ay (±57.7) (min-maks 1-212)'di. 25 hastada kritik hiponatremi olarak tanımlanabilecek 125 mEq/L'nin altında serum sodyumu vardı. Ortalama sodyum 131 (±3.3) mEq/L (min-maks: 109-134)'dü. Serum kreatinin düzeyleri tedavi öncesi ve tedavi sonrası anlamlı farklılık gösterdi (p<0.001). Hiponatreminin ortalama düzelme süresi 2.1 gün (±1.29) (min-maks: 1-12)'di. Toplam 23 hastada serum sodyumu 125 mEq/L ve altındaydı. Takipleri sonunda tüm hastalarda mortalite oranı %23'tü.

Sonuç: Hiponatremi çocuk yoğun bakım ünitelerinde sık görülen bir sorundur. Özellikle ciddi hiponatremi artmış mortalite ile ilişkilendirilebilir. Akciğer enfeksiyonlarında, travma hastalarında ve santral sinir sistemi patolojilerinde serum sodyumunun yakından izlenmesi gerekmektedir.

Anahtar Sözcükler: Çocuk, Hiponatremi, Sodyum

INTRODUCTION

Hyponatremia is defined as having a serum sodium level below 135 mEq/L, and a serum level below 125 mEq/L is generally considered serious. It is one of the most common electrolyte disorders, and is associated with increased morbidity and mortality especially in critically ill patients. Underlying medical conditions may worsen the prognosis (1).

Hyponatremia is accepted as an independent risk factor in pediatric intensive care units. Many factors such as dehydration, gastrointestinal losses, central nervous system pathologies, acute or chronic kidney injury, syndrome of inappropriate antidiuretic hormone secretion (SIADH) and incorrect replacement solutions are blamed in the pathogenesis of hyponatremia (2).

Hyponatremia may cause cerebral edema and neurologic symptoms. If correction is made too quickly, osmotic demyelination syndrome (formerly known as central pontine myelinolysis) will occur. Fluid resuscitation is very important in critically ill patients, as sudden increases or decreases in serum sodium levels can cause severe changes in the central nervous system (3).

Early diagnosis and prompt treatment are essential to prevent morbidity and mortality. In order to treat hyponatremia properly, the patient's volume status, etiology of hyponatremia and underlying problems should be known. In this study, we aimed to investigate the etiology and prognosis of hyponatremia in a tertiary pediatric intensive care unit.

MATERIALS and METHODS

Study Population and Collection of The Data

We retrospectively evaluated pediatric patients with hyponatremia in the tertiary pediatric intensive care unit at Kayseri City Hospital between June 2018 and December 2020. Hyponatremia was accepted as having serum sodium less than 135 mEq/L. Critical hyponatremia was defined as having serum sodium less than 125 mEq/L. Resolution of hyponatremia was defined as a rise in serum sodium above 135 mEq/L. If there was hyponatremia in repeated hospitalizations, the last hospitalization of the patient was included. The available data of 342 patients were recoded. Data on primary diagnoses, treatment options, length of hospital stay, and mortality were analyzed. Annual mortality rate of the tertiary pediatric intensive care unit was obtained from the hospital's records.

Statistical analysis

Analysis of data from 342 pediatric patients with hyponatremia performed with IBM SPSS for Windows version 17. The normality of numerical variable distributions was evaluated with the Shapiro-Wilk test. Student's t-test was performed in normally distributed data. The Mann-Whitney U test was used to compare data with skewed distributions. Frequency and percentages were used as descriptive values in categorical data. Arithmetic mean ± standard deviation was used for normally distributed data, median and interquartile range were used for non-normally distributed data. p-value <0.050 was considered significant.

The study was carried out with the approval of Kayseri City Hospital Ethics Committee, dated 18.03.2021 and project number 332.

RESULTS

We reviewed the records of 342 patients. The male/female ratio was 192/150 (56.1% vs. 43.9%). The mean age of the patients was 41.78 months (±57.7) (min-max 1-212). Twenty-five patients had serum sodium below 125 mEq/L, which could be defined as critical hyponatremia. The mean sodium was 131 (±3.3) mEq/L (min-max: 109-134). The lowest serum sodium was 109 mEq/L. The mean post-treatment serum sodium was 137.9 (±2.8) (min-max: 127-163). There was a significant difference between serum sodium levels before and after treatment (p<0.001).

At the time of detection of hyponatremia, the mean serum creatinine was 0.56 mg/dL (±1.07) (min-max: 0.02-13.15). After treatment, mean serum creatinine was 0.45 mg/dL (±0.6) (min-max: 0.01-4.82). The levels of serum creatinine significantly differs before and after treatment (p<0.001).The highest serum creatinine value of 13.15 mg/dL was found in a patient with chronic kidney disease due to bilateral kidney dysplasia, the

patient underwent peritoneal dialysis and the control serum creatinine value was 3.3 mg/dL. The lowest serum sodium (109 mEq/L) in this cohort belonged to the same patient.

The mean serum potassium level at the time of hyponatremia is 4.3 mEq/L (Min-max: 2.3-8.2). Twenty-four patients had hyperkalemia (serum potassium was above 5.5 mEq/L).

Severe hyperkalemia (serum potassium ≥6.5 mEq/L) was present in 4 patients. One of these patients had pseudohypoaldosteronism, serum sodium was 126 mEq/L and serum potassium was 6.8 mEq/L. Electrolyte values returned to normal in the follow-up with treatment. Two patients had acute renal failure and one patient was being followed up after sudden arrest.

There were 4 patients with severe hypokalemia (serum potassium ≤2.5 mEq/L). Two of them had been diagnosed with cystic fibrosis, one with neurometabolic disease, and one with maple syrup urine disease.

There were 5 patients with serum chloride below 80 mEq/L. Two of these patients had cystic fibrosis (patients with severe hypokalemia), one had undergone necrotizing enterocolitis operation and the other had surgery for perforated appendicitis. The other was the chronic kidney disease patient requiring dialysis, who had the lowest sodium and highest creatinine values in the cohort. When the urine densities were examined, there were 10 patients with a urine density of 1040 and above. Five had trauma. Fluid restriction was performed in two of these ten patients, considering SIADH in the follow-up.

When the primary diseases of the patients and the underlying diagnoses were evaluated, it was documented that the most common ones are infectious diseases (bronchopneumonia in 60 patients, bronchiolitis in 25 patients, acute gastroenteritis in 16 patients, etc.). Neurological problems are the next common one. Cerebral palsy was seen in 12 patients, epilepsy in 13 patients, and status epilepticus in another 12 patients. Eighteen patients had an established diagnosis of hereditary and metabolic disease. Intoxication was the reason of hospitalization in 16 patients, whereas 14 patients had trauma. 16 patients with diabetic ketoacidosis had hyponatremia. Cardiac problems were seen in 12 patients. Hematologic malignancies were the reason of hospitalization in 11 patients. Kidney diseases were the primary diagnosis in 10 patients including 5 hemolytic uremic syndrome patients (Table I).

The reasons for admission to the pediatric intensive care unit were respiratory distress in 142 patients (41.5%), shock in 42 patients (12.3%), severe dehydration in 24 patients (7%), acute kidney injury in 8 patients (2.4%), and trauma in 14 patients (4.1%) (Table II). In most of the cases, the exact cause of hyponatremia cannot be detected from the medical records of the patients. Hyponatremia was associated with dehydration in 69 patients (20.2%), acute kidney injury in 22 patients (6.4%), SIADH in 10 patients (2.9%), central salt wasting in 3 patients

Table I: Diagnoses of the patients

Disease	Patient number (n)
Infectious diseases	
Bronchopneumonia	60
Bronchiolitis	25
Acute gastroenteritis	16
Rash&erythema	3
Sepsis	2
Meningitis	1
Meningoencephalitis	1
Neurological diseases	
Cerebral palsy	12
Epilepsy	13
Status epilepticus	12
Spinal muscular atrophy	2
Hypoxic ischemic encephalopathy	3
Guillain-Barre Syndrome	1
Kidney diseases	
aHUS	1
HUS	4
Acute renal failure	2
Chronic kidney disease	2
Posterior urethral valve	1
Hematological malignancies	
ALL	9
AML	2
Diabetic ketoacidosis	16
Cardiac issues	
Aortic coarctation	2
Dilated cardiomyopathy	4
Fallot tetralogy	3
Arrythmia	3
Post-arrest	7
Trauma	14
Intoxication	16
Hereditary and Metabolic Diseases	18
Other	89
Total	342

aHUS: *Atypical hemolytic uremic syndrome,* ***HUS:*** *Hemolytic uremic syndrome,* ***ALL:*** *Acute lymphoblastic leukemia,* ***AML:*** *Acute myeloid leukemia*

(0.9%), and incorrect replacement solution in one patient (Table III). Five among ten patients with SIADH had bronchiolitis/bronchopneumonia, and two patients had neurologic problems.

The treatment options were intravenous electrolyte replacement in 313 patients (91.5%), fluid restriction in 10 patients (with SIADH) (2.9%), oral sodium chloride administration in 19 patients (5.6%). Electrolyte replacement were made according to the patients' clinical status and age. Deficit treatments were administered when necessary.

The mean resolution time of hyponatremia was 2.1 days (±1.29) (min-max: 1-12). The median recovery time from hyponatremia was 2 days. The mean resolution time of hyponatremia in patients with serum sodium above 130 was 1.9 (±1.1) (min-max: 1-9) days. Recovery time of hyponatremia was significantly

Table II: The reason of the need for pediatric intensive care unit hospitalization

Cause	Frequency	Percent
Respiratory problems	142	41.5%
Shock	42	12.3%
Severe dehydration	24	7%
Acute kidney injury	8	2.4%
Trauma	14	4.1%
Others	112	32.7%
Total	342	100.0

Table III: Detected cause of hyponatremia

Cause	Frequency	Percent
None	237	69.3
Dehydration	69	20.2
Acute kidney injury	22	6.4
SIADH	10	2.9
Central salt loss	3	0.9
Wrong solution	1	0.3
Total	342	100.0

shorter in patients with serum sodium closer to normal range (p<0.010).

Serum sodium was 125 mEq/L and below in a total of 23 patients. Mortality was recorded in 4 of 23 patients whose serum sodium level was below 125 mEq/L. When we excluded other obvious causes of mortality (such as serious neurometabolic diseases, post-arrest patients, severe cardiac anomalies), there was a correlation between low serum sodium and increased mortality risk (p=0.050). Recovery time was longer in patients with critical hyponatremia (p<0.001). No correlation was found between serum sodium level below 125 mEq/L and length of hospital stay.

Average length of intensive care unit stay is 30.3 days (±65) (min-max: 1-480). The median hospital stay was 7 days. There were 13 patients with a hospital stay of 180 days or more. Mortality was recorded in 6 of them at follow-up. Mortality was found to be higher in patients with a long hospital stay and this was statistically significant. The mean sodium level of these patients was 132 mEq/L, and two had chronic lung disease (one with tracheostomy), one had spinal muscular atrophy, one had hydrocephalus, one had epilepsy, two had a diagnosed syndromic condition, and two had hypoxic ischemic encephalopathy. Most of the patients with long hospitalizations had genetic, neurological or metabolic disease.

It was recorded that 81 of 342 patients died due to various reasons at the end of the hospitalization period. The mortality rate was determined as 23% in patients who were found to have hyponatremia during one period of intensive care hospitalization. According to the data obtained from the medical records of the hospital, the annual mortality rate in the tertiary intensive care unit at the time of the study was 60 in 766 patients and the mortality rate was 8%.The mortality rate in patients with hyponatremia during intensive care hospitalization was found to be significantly higher than general intensive care mortality.

Table IV: Treatment choices for hyponatremia

Treatment	Frequency	Percent
Intravenous electrolyte replacement	313	91.5
Fluid restriction	10	2.9
Oral sodium chloride administration	19	5.6
Total	342	100.0

A correlation could not be established between the admission sodium value, the total length of hospital stay and the rate of mortality (p>0.050). However, there was a relationship between critical hyponatremia (serum sodium ≤125mEq/L) and mortality (p=0.050). It was noted that critical hyponatremia prolonged the recovery day of hyponatremia but did not affect the total hospitalization time.

DISCUSSION

Hyponatremia is a common problem in pediatric intensive care units, and is associated with increased mortality (4,5). Although the main outcome of prognosis can be attributed to the primary disease; hyponatremia and electrolyte imbalances may contribute to increased mortality (1).

In a study, it was stated that 32.4% of patients with serum electrolyte disorders in the pediatric emergency department needed an admission to the pediatric intensive care unit (6). Fluid resuscitation is very important in critically ill patients because an abrupt increase or decrease in serum sodium levels can cause severe changes in the central nervous system (2).

Children are more prone to hyponatremia, especially when hospitalized for respiratory and central nervous system infections such as pneumonia or meningitis. Lung diseases such as bronchopneumonia and bronchiolitis can lead to SIADH by unclear mechanisms, and nervous system abnormalities can cause antidiuretic hormone secretion from the pituitary. SIADH is also more common in hospitalized, post-operative patients due to administration of hypotonic fluids, medications, and the body's response to stress (7,8). Ten patients with SIADH in our cohort, responded well to fluid restriction. Tolvaptan may be indicated in cases which do not respond to fluid restriction (9).

Hyponatremia is a common finding in patients with intracranial problems such as trauma or hemorrhage and is associated with increased mortality, and length of stay in intensive care units. Its diagnosis and treatment are essential for prompt neurocritical care (3). In addition to trauma patients and central pathologies, sodium should be closely monitored, especially in patients

with bronchopneumonia (10,11). Luu et al. (12) concluded that hyponatremia may worsen the prognosis in children with bronchiolitis in the pediatric intensive care unit.

The most common cause of serum sodium abnormality in neurocritical patients is SIADH, a clinical entity that can be underestimated and therefore poorly treated, early diagnosis is essential to prevent complications (1). In our cohort most of the patients with hyponatremia had bronchopneumonia/bronchiolitis (24.8%). Besides, half of ten patients with SIADH had bronchopneumonia/bronchiolitis.

Acute gastrointestinal losses due to acute gastroenteritis, as well as diarrhea and vomiting, are another important cause of hyponatremia and one of the leading diagnoses in our cohort. Dehydration can occur not only from gastrointestinal losses, but also from failure of oral nutrition in a severely injured or sick child. When we tried to figure out the cause of hyponatremia, we found dehydration in about 20% of the patients.

Most of the patients in our study had serious chronic comorbidities including metabolic diseases and neurological diseases. This might explain the high mortality rate in our cohort. Among 16 patients with diabetic ketoacidosis hyponatremia was detected. Since hyperglycemia and hypertriglyceridemia can cause pseudohyponatremia, this may be a false low sodium result.

Kidney diseases can cause hyponatremia. Especially in dialysis patients, fluid overload may occur and dilutional hyponatremia may be encountered. Additionally, pseudohypoaldosteronism is a serious problem, manifested by low serum sodium and high serum potassium despite normal to high aldosterone levels. One of the important causes of pseudohypoaldosteronism is congenital anomalies of the kidney and urinary tract such as hydronephrosis.

In addition to hyponatremia, if the patient has hypokalemia and hypochloremia with metabolic alkalosis the physician should be careful about renal tubular diseases such as Bartter's Disease, or a case of pseudobartter, which is usually seen in cystic fibrosis. Two of our patients with hypokalemia and hypochloremia accompanying hyponatremia had cystic fibrosis.

The significant decrease in the serum creatinine value of our patients can be explained by the fact that some of the patients were dehydrated at admission and had prerenal acute renal failure that subsequently recovered rapidly with volume replacement.

Serum electrolyte abnormalities were demonstrated to be associated with longer stay in pediatric intensive care unit, however we could not show such correlation (13). We showed that mortality rate was higher in patients with a long hospital stay.

Mortality of hyponatremia in pediatric intensive care unit is reported up to 37.7% (14). In our study, we found the mortality rate to be 23% in hyponatremia patients hospitalized in the tertiary pediatric intensive care unit, and this mortality rate is obviously high when compared to the annual death rate of the pediatric intensive care unit.

The limitations of our study arise from its retrospective nature. Since we selected the study group only as hyponatremic patients with available data in the medical records, we could not give an exact prevalence of hyponatremia in general hospitalizations in pediatric intensive care unit. Also we could not determine which infusion solutions were given to the patients in the first applications. Furthermore, the true prevalence of hyponatremia in such critically ill patients is difficult to document, as most of the patients receive intravenous infusion (especially saline) in the emergency room or inpatient clinic before being admitted to intensive care (15,16). In most of the patients, information about the cause of hyponatremia could not be obtained from the system notes and laboratory records. Keeping proper records is also very important.

CONCLUSIONS

The patients with hyponatremia needs a cautious approach. Etiology and exact causes should be documented in order to ameliorate the electrolyte imbalances, in especially hyponatremia. Since hyponatremia is associated with increased mortality, prompt treatment is important. The treatment should be planned carefully and precisely in order to prevent central nervous system complications. Further prospective studies were necessary to document the effects of sodium imbalances in critically ill children.

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