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Original Paper

Incidence of Hospital-Acquired Hyponatremia and its Risk Factors in Hospitalized Children: A Longitudinal Study

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Introduction. Hyponatremia in hospitalized children is associated with several clinical complications. This study aimed to evaluate the incidence and risk factors of hospital-acquired hyponatremia in pediatric patients.
Method. A longitudinal study was conducted between 2016 and 2020 on hospitalized children who were admitted in Dr Sheikh Hospital, Mashhad University of Medical Sciences, Iran with normal serum sodium levels. Patients were followed for hyponatremia and its risk factors during hospitalization. Demographic data, clinical symptoms, underlying disease, type of serum, ward of hospitalization, and final diagnosis were recorded. Patients with incomplete blood samples or abnormal serum level of sodium at the time of admission were excluded.
Result. A total of 456 children, including 267 males (58.6%) with a mean age of 69.40 ± 42.42 months were studied. The incidence of hyponatremia was 22.1%. The female sex (3.83 (95% confidence interval: 1.08, 13.59)) was the independent risk factors of hyponatremia. Children less than one year of age (2.68 (95% confidence interval: 0.97, 7.42) P = .057), were also borderline significant for the risk of hyponatremia.
Conclusion. The incidence of hospital-acquired hyponatremia was 22.1%. The female sex was the independent risk factor of hyponatremia. Children less than one year of age may also be at risk for hyponatremia. Further studies are needed to confirm these findings.

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INTRODUCTION

Hyponatremia, defined as serum sodium levels below 135 mEq/L, is a common electrolyte disorder in children.[1] There are serious concerns regarding hyponatremia in hospitalized children, because it is associated with neurological complications including impaired level of consciousness, seizure, encephalopathy and increased risk of mortality. Hospitalized patients with concomitant hyponatremia may require more mechanical ventilation and intensive care resulting in prolonged hospital stay and increased risk of mortality.[2-4] There are several studies on the incidence of hospital-acquired hyponatremia (HAH) in adults.[5-7] However, data reporting the incidence of HAH in children are relatively low. A study conducted in Japan showed that the incidence of hyponatremia in hospitalized children was 17%.[8] The frequency was increased up to 45% in hospitalized children with pneumonia in Italy.[9]

Research on the incidence of hospital-acquired hyponatremia in Iranian children is insufficient, therefore, this longitudinal study investigated the incidence and risk factors of hospital-acquired hyponatremia in children admitted to a tertiary hospital in Mashhad University of Medical Sciences, Mashhad, Iran.

MATERIALS AND METHODS

The present longitudinal retrospective cohort study, was conducted at Dr Sheikh Hospital, Mashhad University of Medical Sciences, Iran. Medical records were examined between 2016 to 2020. The study population was hospitalized children who were admitted with normal sodium levels. Patients were followed up for hyponatremia during the hospitalization. This study carried out in compliance with declaration of Helsinki. Study protocol approved by the Ethics Committee of Mashhad University of Medical Sciences (code: IR.MUMS.MEDICAL.REC.1399.305).

A total of 456 hospitalized children aged 1 month to 16 years old were included using non-random sampling. The first sampling was at the time of admission and the second sampling was carried out 48 hours later.

A serum sodium level of 135–145 mEq/L was regarded as normal. Hyponatremia was defined as a serum sodium level of less than 135 mEq/L, and hypernatremia as a serum level of more than 145 mEq/L. Each patient's age, sex, serum potassium and sodium concentrations, body temperature, medical symptoms, final diagnosis, underlying medical history, hospital ward, type of serum administered, and medications were among the information gathered. Fever was defined as a body temperature of 37.5°C or greater based on axillary measurement. A body temperature greater than 38.5°C was considered a severe fever. Atomic absorption spectrophotometry was used to measure the serum sodium concentrations.

Sample size

The sample size was calculated at 456 patients according to the incidence of hyponatremia in hospitalized children reported in the Bibi study as 0.47%.[10] Alpha was considered 0.05.

Statistical Methods

Data was analyzed using SPSS program version 22 (SPSS Institute, Inc., Chicago, IL, USA). All characteristics of the patients were described as means ± standard deviation (SD), median and interquartile range (IQR) or frequency. Normal distribution was verified using kolmogorov-smirnov test. The relationship between qualitative variables was evaluated using chi-square test. Comparison between two groups was performed using independent sample t testing or its nonparametric equivalent. Strength of association was determined by risk ratio (RR) 95% confidence intervals (CIs) using logistic regression. A *P*-value less than .05 were considered significant.

RESULTS

Demographic and baseline characteristics

A total of 456 children, 267 of them were males. The mean age of patients was 69.40 ± 42.42 months. Fever was the most common clinical symptom (n = 191, 41.9%), followed by vomiting (n = 80. 17.5%). The most common diagnosis was respiratory diseases including pneumonia and bronchiolitis (n = 118, 25.93%). Two hundred and seventeen children (47.6%) were admitted in the emergency department. Hypotonic solution (1/2 normal saline) was used in 411 children (90.7%). Baseline characteristics in total population and according to sex of patients are presented in Table 1.

Serum sodium level measurements

At the time of admission, all of the children had normal sodium levels; however, 347 of them remained isonatremic (76.1 percent) at the end of the follow-up, and 22.1 percent (n = 101) experienced hyponatremia while in the hospital. The mean serum sodium levels at the time of admission and the end of the follow-up were 139.26 ± 2.64 and 137.55 ± 4.64 mEq/L. The serum sodium level at the end of follow-up in hyponatremic and isonatremic patients was 130.89 ± 3.47 and 139.22 ± 2.42 mEq/L, respectively. A total of 404 patients exhibited normal serum potassium levels upon admission (88.6%), whereas 39 patients (8.6%) were hypokalemic. Four hundred twenty-four patients (93%) had normal potassium level, while 24 patients (5.3%) remained hypokalemic at the end of the follow-up. Table 2, shows the baseline characteristics of patients with and without hyponatremia.

The frequency of respiratory diseases in patients with and without hyponatremia was 10 (26.4%)

Table 1. Baseline characteristics of patients

Variables	Sex		Total (n = 456)
	Males (n = 267)	Females (n = 189)	
Age (month)	70.27 ± 41.50	68.17 ± 43.56	69.40 ± 42.42
Body temperature			
No fever	152 (56.9%)	113 (59.8%)	265 (58.1%)
Mild-moderate fever	105 (39.3%)	69 (36.5%)	174 (38.2%)
Severe fever	10 (3.7%)	7 (3.7%)	17 (3.7%)
Clinical symptoms			
Vomiting	47 (17.6%)	33 (17.5%)	80 (17.5%)
Pain	49 (18.4%)	23 (12.2%)	72 (15.8%)
Diarrhea	38 (14.2%)	25 (13.2%)	63 (13.8%)
Narcotic consumption	34 (12.7%)	16 (8.5%)	50 (11%)
Final diagnosis			
Respiratory	60 (22.6%)	58 (30.7%)	118 (25.93%)
Hematologic	66 (24.8%)	39 (20.6%)	105 (23.59%)
CNS	17 (6.4%)	10 (5.3%)	27 (5.93%)
Urinary	38 (14.3%)	18 (9.5%)	56 (12.30%)
Gastrointestinal	28 (10.5%)	24 (12.7%)	52 (11.42%)
surgery	10 (3.8%)	4 (2.1%)	14 (3.1%)
Others	47 (17.7%)	36 (19%)	83 (18.24%)
Underlying disease			
Hematological	95 (55.9%)	51 (43.6%)	146 (50.87%)
Respiratory	26 (15.3%)	24 (20.5%)	50 (17.42%)
Renal	20 (11.8%)	21 (17.9%)	41 (14.28%)
Neurological	6 (3.5%)	4 (3.4%)	10 (3.48%)
Endocrine	0	2 (1.7%)	2 (69%)
Others	23 (13.5%)	15 (12.8%)	38 (13.24%)
Type of fluid therapy			
Hypotonic	227 (89.7%)	162 (91%)	411 (85.9%)
Isotonic	19 (7.5%)	9 (5.1%)	28 (6.2%)
No fluid therapy	7 (2.8%)	7 (3.9%)	14 (3.1%)
Admission wards			
Emergency	126 (47.2%)	91 (48.1%)	217 (47.6%)
Hematology	75 (28.1%)	45 (23.8%)	120 (26.3%)
Nephrology	52 (19.5%)	39 (20.6%)	91 (20%)
Surgery	7 (2.6%)	4 (2.1%)	11 (2.4%)
General	2 (0.7%)	7 (3.7%)	9 (2%)
ICU	5 (1.9%)	3 (1.6%)	8 (1.8%)

SD: standard deviation, CNS: central nervous system, ICU: intensive care unit

and 40 (17.7%), respectively. The frequency of central nervous system CNS disorders including febrile seizure and meningitis in patients with and without hyponatremia was 2 (3.3%) and 8 (3.5%), respectively. The frequency of renal diseases including urinary tract infection (UTI) and glomerulonephritis in patients with and without hyponatremia was 15 (24.6%) and 26 (11.5%), respectively. The frequency of hematologic disorders including acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) and other hematologic cancers was 26 (42.6%) and 120 (53.1%) in patients with and without hyponatremia, respectively. The frequency of endocrine diseases including type I diabetes mellitus was 1 (1.6%) and 1 (0.4%) in patients with and without hyponatremia, respectively. The frequency of other diseases such as gastroenteritis, cardiac disease including ventricular septal defect (VSD) and Down syndrome was 7 (11.5%) and 31 (13.7%) in patients with and without hyponatremia, respectively. The relationship between the underlying disease and the incidence of hyponatremia was not significant (P = .15).

Children under two years old (n = 84) had a higher prevalence of hyponatremia than those

Table 2. Comparison of baseline characteristics between patients with and without hyponatremia

Variable	Groups		*P*
	Without hyponatremia (n = 355) Frequency (%)	With hyponatremia (n = 101) Frequency (%)	
Sex			
male	218 (61.4%)	49 (48.5%)	.02
female	137 (38.6%)	52 (51.5%)	
Body temperature			
Without fever	205 (57.7%)	60 (59.4%)	
Mild-moderate fever	137 (38.6%)	37 (36.6%)	.95
severe fever	13 (3.7%)	4 (3.96%)	
Clinical symptoms			
Vomiting	57 (16.1%)	23 (22.8%)	.17
Pain	54 (15.2%)	18 (17.8%)	.52
Diarrhea	45 (12.7%)	18 (17.8%)	.18
Narcotic consumption	40 (11.3%)	10 (9.9%)	.69
Type of IV fluid			
Isotonic	25 (7.1%)	3 (3%)	
Hypotonic	314 (89.2%)	97 (96%)	.10
No serum therapy	13 (3.7%)	1 (1%)	
Admission ward			
Emergency	170 (47.9%)	47 (46.5%)	
Nephrology	67 (18.9%)	24 (23.8%)	
Hematology	101 (28.5%)	19 (18.8%)	.01
General	8 (2.3%)	1 (1%)	
ICU	3 (0.8%)	5 (5%)	
Surgery	6 (1.7%)	5 (5%)	
Age (month)	72.40 ± 61.03	58.48 ± 10.47	.01**

*Chi-square test
**T-test

two years or older (n = 372, 39.3% versus 18.3%, *P* = .01). Children under one year old (n = 53) had a higher prevalence of hyponatremia than children one year or older (n = 403, 45.3% versus 19.1%, *P* = .01). In children under 12 months (n = 53) and those between 12 and 24 months (n = 33), the prevalence of hyponatremia was 45.3% and 27.3%, respectively (*P* = .09).

Risk factors of hyponatremia

Women were more likely than men to develop HAH, according to multiple logistic regression (RR = 3.83, 95% CI: (1.08, 13.59), *P* = .03). Compared to patients between the ages of 12 and 24 months, those under the age of 12 months showed a slightly increased risk of developing HAH.

(RR = 2.68, 95% CI: (0.97, 7.42), *P* = .057). The risk of HAH was not significantly correlated with any other variables. Data are presented in Table 3.

DISCUSSION

The current longitudinal study was conducted

Table 3. Risk factors of hospital-acquired hyponatremia in children

Variable	RR (95% CI)	*P*
Female sex	3.83 (1.08, 13.59)	.03
Vomiting	0.78 (0.05, 12.12)	.86
Diarrhea	1.92 (0.40, 9.21)	.41
Diagnosis of respiratory, neurological and surgical diseases (reference: other diagnoses)	1.17 (0.31, 4.42)	.80
Hypotonic solution (reference: isotonic solution)	2.97 (0.37, 28.2)	.30
Age group under 1 year	1.56 (0.42, 5.79)	.50
Age group under 2 years	1.45 (0.48, 4.38)	.50
Age less than 1 year (reference: 12-24 months)	2.68 (0.97, 7.42)	.057

RR: risk ratio, CI: confidence interval

between 2016 and 2020 to assess the incidence and risk factors of hospital-acquired hyponatremia (HAH) in children. As mentioned earlier the incidence of HAH was 22.1%. Patients in the emergency room, females, and younger children were more at risk to develop HAH.

Hyponatremia is an important electrolyte disturbance in children, since it may be associated with serious neurological complications. However, studies on the incidence of hyponatremia in hospitalized children are limited. Our study was the first on this important topic in Iranian children.

The incidence of HAH has been reported between 9% and 50% in different studies based on the definition of hyponatremia, inclusion criteria, and comorbidities,[11-13] which closely aligns with our study, revealing an incidence of 22.1% among our studied group. In a study performed in the United States on 1048 hospitalized children with normal sodium levels, the incidence of HAH was 35%,[11] whereas acquired hyponatremia was reported in 9.2% of children in a study conducted in Canada on 432 hospitalized children. This study was linked to the type of fluid therapy used during hospitalization.[12] On the other hand, Stelfox *et al.*, in another study, reported the incidence of hyponatremia (defined as serum sodium less than 133 mEq/L) of 11% in patients admitted to the intensive care units (ICUs).[13]

The type of fluid therapy is reported to be an important factor in the development of HAH in several studies.[14,15] However, we could not establish an association between the type of fluid therapy and the development of HAH. It may be partially caused by the regulating mechanisms of sodium reabsorption in kidneys, which prevent sodium excretion through kidneys. A study by Velasco *et al.* reported that isotonic intravenous fluids had the least correlation with HAH development in children under 15 years in ICU wards. According to this study, 41.2% of patients who received hypotonic fluids were hyponatremic; whereas 18.6% of patients treated with isotonic fluids, developed hyponatremia.[16] In our study, 96% of children with HAH received hypotonic solution, however, 89.2% of children who received hypotonic solutions did not develop hyponatremia.

Bibi *et al.*, found that the majority of hyponatremic patients were hospitalized children with gastrointestinal disorders.[10] However, in our study, we found no association between the underlying disease and hyponatremia. Although we found that hyponatremia is significantly more prevalent in ICU admitted patients compared to patients that were admitted in general and emergency wards (62.5% versus 11.1% and 21.7%, respectively), we could not perform regression analysis to calculate the risk of HAH, because of small sample size in the general and ICU subgroup of patients.

Some studies have reported the impact of age on the development of HAH. Berhanu *et al.* showed that in children under age of 5 was 2.37 times higher risk of HAH than in children between the ages 5 to 15.[17] According to our findings, the incidence of HAH was higher in children less than 2 years. Additionally, we discovered that, in comparison to those aged 12 to 24 months, those under one year had a borderline significant risk of developing hyponatremia. The higher incidence of HAH in younger children may be due to immature mechanisms of sodium re-absorption in the kidneys. However, the impact of younger age on the risk of developing HAH needs further studies. Interestingly, in our study we found that females had an increased risk of developing HAH, although we do not have an exact cause or mechanism for this observation; future research warrants for whether there is a valid explanation.

Encephalopathy or impaired mental function is an important complication of hyponatremia, which may lead to irreversible brain damage. However, due to a lack of large prospective studies, reports about this important complication are rare. In several studies the incidence of hyponatremic encephalopathy in children with serum sodium levels below 125 mEq/L was 53%, 60%, and 78%, respectively.[18-20] In our study, we have no hyponatremic encephalopathy. It might be due to the presence of few patients with severe hyponatremia (serum sodium level less than 125 meq/L) in our study population.

CONCLUSION

The incidence of hospital-acquired hyponatremia was reported to be 22.1% in our study. The female sex was an independent risk factor of hyponatremia. Children less than one year of age may also be at increased risk for hyponatremia. More studies are needed to confirm this observation.

Ethics approval and consent to participate

All patients were included after obtaining written informed consent from parents or legal guardians. Mashhad University of Medical Sciences ethics committee approved this study (code: IR.MUMS.MEDICAL.REC.1399.305).

CONSENT FOR PUBLICATION

All authors agree to publish the article.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

AVAILABILITY OF DATA AND MATERIAL

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request

CODE AVAILABILITY

Not applicable.

- There is appropriate permission for reproduced images.

AUTHORS' CONTRIBUTIONS:

Farhad Heydarian, Elham Bakhtiari, Adeleh Azarshab: conception or design

Elham Bakhtiari, Sara Saadat, Farhad Heydarian: acquisition, analysis

Elham Bakhtiari, Farhad Heydarian, Adeleh Azarshab, Sara Saadat: drafting the work

Elham Bakhtiari, Farhad Heydarian, Adeleh Azarshab, Sara Saadat: final approval

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