Does Serum Chloride Level Affect the Outcomes in Children Admitted to the Pediatric Intensive Care Unit?

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Abstract

Background: Serum chloride disorders are common in critically ill patients and appear to be associated with worse outcomes in patients. However, less attention has been paid to the amount of chloride in critically ill patients. This study aims to determine the frequency of serum chloride disorders and their possible association with disease outcomes in all children admitted to the pediatric intensive care unit (PICU).

Methods: This prospective study was performed on all patients admitted to the PICU of Akbar Children Hospital, Mashhad, Iran, from April 2019 to April 2020. Serum chloride levels were recorded daily on the first, second, and third days of the PICU stay. Statistical analyses were carried out using SPSS software (Version 24, SPSS Inc., Chicago, IL, USA) through one-way analysis of variance, t-test, and Chi-square test in the significance level of $\alpha=0.05$.

Results: In this study, no significant relationship was observed between serum chloride levels and patients' final status ($P\geq0.05$). Serum Chloride level on the first day of PICU admission was significantly correlated with the length of PICU stay (r= 0.258, P= 0.029). There was no significant relationship between serum chloride levels and the patients' need for mechanical ventilation on any of the three days ($P\geq0.05$).

Conclusions: According to the results, serum chloride level can be considered as an indicator of the length of the PICU stay.

Key Words: Child, Chlorides, Intensive Care Units, Pediatrics.

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1- INTRODUCTION

Chloride ion is the most abundant anion in plasma and interstitial fluid. Although chloride is one of the main electrolytes that are routinely and daily monitored in hospitalized patients, less attention has been paid to chloride levels in patients with critical conditions (1). Serum chlorine disorders are common in critically ill patients and appear to be associated with worse outcomes in patients (2). Chloride concentration in plasma ranges from about 97 to 107 mmol/L. Chloride is vital for electrical neutralization of serum, acid-base balance, fluid homeostasis, osmotic pressure, production of hydrochloric acid in the gastrointestinal tract, kidney function, and electrical functions of cells, for example, in muscle activity (3, 4). Chloride has been identified as a major cause of anion-free metabolic alkalosis and metabolic acidosis in critically ill patients (5). Numerous studies have shown that chloride deficiency stimulates renin secretion and ultimately increases systemic blood pressure (6). Administration of sodium chloride solution 0.9% can cause hyperchloremic metabolic acidosis which results in decreased renal blood flow, impaired immune function, and even death (7).

Serum chlorine disorders are common in critically ill patients and appear to be associated with worse outcomes in patients (2). Hypochloremia and hyperchloremia usually refer to chloride levels less than 96-101 mmol/L and higher than 106-111 mmol/L,respectively (8,9). Hypochloremia in patients with critical conditions may be due to active chloride loss caused by vomiting, diarrhea, inadequate renal reabsorption, or decreased concentration following infusion of hypotonic fluids (10). Hyperchloremia occurs in patients with critical conditions related to the loss of bicarbonate from the gastrointestinal tract or kidneys (5, 11). Hyperchloremia is very common in critically ill patients; however, this issue is still under investigation. Some studies have shown that transient hyperchloremia may occur in about 75% of ICU patients during the first 24 hours of ICU admission (12).This study aimed to determine the possible relationship between this disorder and the outcome in children admitted to the pediatric intensive care unit (PICU).

2- MATERIALS AND METHODS

In this prospective study, all children admitted to the PICU of Akbar Children Hospital, Mashhad, Iran, were examined for a period of one year from April 2019 to April 2020. Data were collected from patients' medical records and the health information registration system. The main outcomes of patients in this study included mortality rate, duration of mechanical ventilation, and length of the PICU stay.

All children in the age range of one month to eighteen years who were admitted to the PICU were included in this study. The included children were required to be NPO (no eating or drinking).

Serum chlorine levels were measured in all patients at the time of admission and in the first and second days after hospitalization and in case of surgery at the time of admission, and in the first and second days after surgery. In each sampling, the patient's blood (2 cc) was taken by a PICU nurse. Serum chloride levels lower than 96 mEq/L and higher than 106 mEq/L were considered to be hypochloremia and hyperchloremia, respectively. Chlorine anion was measured by the auto analyzer and sodium and potassium ions were measured using ionogram apparatus. All the requested tests were performed in the laboratory of Akbar hospital in Mashhad, Iran. Data were analyzed using SPSS software (Version 24, SPSS Inc., Chicago, IL, USA). The significance level was determined to be less than 0.05 in this study.

2-1. Inclusion and Exclusion Criteria

The inclusion criteria encompassed patients who underwent cardiovascular resuscitation before admission to the PICU, patients with glomerular filtration rate less than 15, patients on dialysis, patients with chronic kidney and liver diseases, patients with malignancy, patients with chronic neurological disorders (e.g., cerebral palsy or seizure disorders being treated), and patients with underlying metabolic disease and heart disease who were under treatment with medication.

Exclusion criteria encompassed children who were hospitalized in the PICU for less than 48 hours, those who received serum other than 0.5 normal saline for any reason, patients who started eating (from days 1-3 of hospitalization in the PICU), and cases who received diuretics.

3- RESULTS

A total number of 189 patients were included in this study, the majority of whom (n=116,61.4%) were males. Moreover,67(35.4%),31(16.4%),and 117(61.9%) patients needed mechanical ventilation, died, and had an underlying disease, respectively. The most common underlying diseases were gastrointestinal, lung, and neurological diseases, and 38% of patients had no underlying or specified underlying disease. The most frequent diagnosis was related to pulmonary (n: 41), neurological (n:39), surgical (n:30), and gastrointestinal diseases (n:30), respectively.

The duration of hospitalization days, duration of PICU stay, and time of mechanical ventilation are presented in **Table 1**.

Table-1: Duration of hospital stay, hospitalization in PICU, and mechanical ventilation

Duration (days)	Mean ± Std	Min	Max
Hospital stay	15.1±16.2	2	113
PICU	5±6.9	2	57
Mechanical ventilation	5.4±7.5	1	40

The frequencies of serum chloride levels in the three days were compared in three categories of low, normal, and high chlorine. The relative frequencies of normal chloride during the three days were estimated at 47.1%, 50.8%, and 53%, respectively. Around half of the patients had normal chloride levels every day. Based on the analysis, the trend of changes in serum chloride levels was not significant in the study population during the three days (P=0.17).

Fig.1 presents the trend of changes in serum chloride levels over three days, with higher changes observed on the second day. Moreover, no significant difference was observed between the living and deceased individuals in terms of the trend of changes in serum chloride levels during the three days (P=0.10).
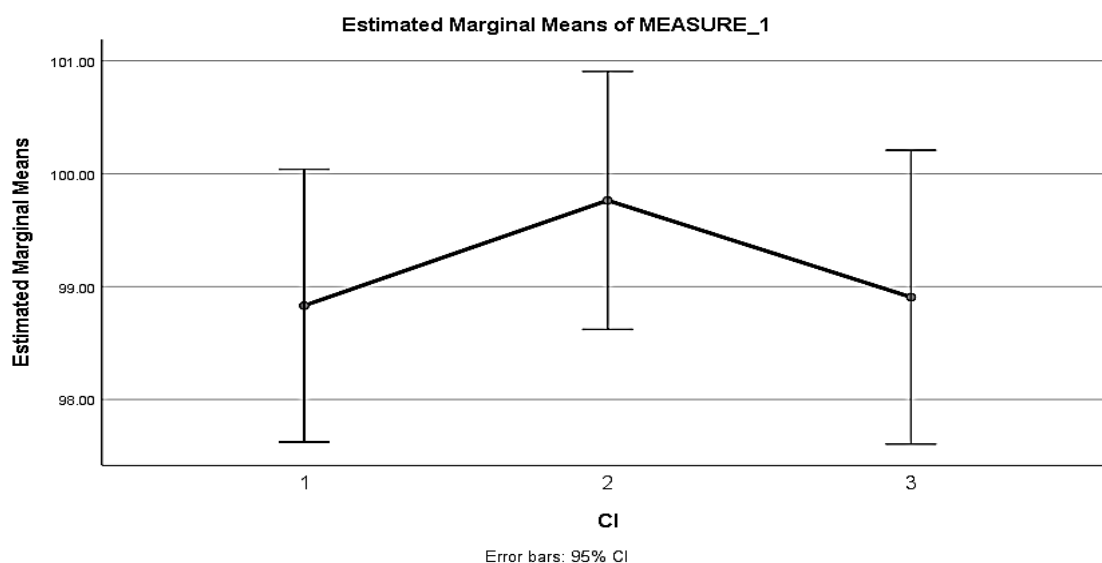
Fig. 1: The trend of changes in serum chloride levels over three days

The serum chloride levels in the two groups of discharged and deceased patients in the three days are tabulated in **Table 2**.

The frequencies of deaths and discharges in each of the low, normal, and high serum chloride categories for each of the three days are presented in **Table 2**. As indicated in this table, 10.1%, 11.5%, and 16.3% of children with normal chloride levels died on the first, second, and third day, respectively.

Table 2. The serum chloride levels according to the final result of patients

		Day 1		Day 2		Day 3	
		Dead	**Discharge**	**Dead**	**Discharge**	**Dead**	**Discharge**
Chloride level N (%)	**Low**	15(22.1)	53(77.9)	13(21.7)	47(78.3)	9(15.5)	49(84.5)
	Normal	9(10.1)	80(89.9)	11(11.5)	85(88.5)	16(16.3)	82(83.7)
	High	7(21.9)	25(78.1)	7(21.2)	26(78.8)	6(20.7)	23(79.3)
	Total	31(16.4)	158(83.6)	31(16.4)	158(83.6)	31(16.8)	154(83.2)
	p-value	0.088		0.175		0.819	
Serum chloride (mmol/L) (Mean±SD)		98.9±11.5	98.8±7.5	99.2±11.6	99.3±9.4	100.9±12.2	98.4±8.1
	p-value	0.97		0.94		0.29	
Serum chloride (mmol/L) (Mean±SD)	**With mechanical ventilation**	98.7±9.5		99.9±9.0		99.4±12	
	Without mechanical ventilation	98.9±7.5		99.0±10.2		98.6±6.7	
	p-value	0.89		0.54		0.62	

No significant relationship was observed between serum chloride levels and patients' final status (P≥0.05).

The serum chloride levels were surveyed in the two groups of patients with and without mechanical ventilation in the first three days of PICU hospitalization. The obtained results showed no significant relationship between serum chloride levels and patients' need for mechanical ventilation on any of the three days (P≥0.05)

Table-3: Correlation between serum chloride level and length of hospital stay, PICU stay, and mechanical ventilation

	PICU stay		Hospital stay		Mechanical ventilation	
	p	r	p	r	p	r
Chloride of the first day	0.029	0.258	0.982	0.002	0.46	0.09
Chloride the second day	0.422	0.096	0.790	0.020	0.54	0.76
Chloride of the third day	0.277	0.131	0.311	0.075	0.7	0.04
PICU stay	-	-	<0.001	0.872	<0.001	0.95
Hospital stay	-	-	-	-	<0.001	0.55
Mechanical ventilation	-	-	-	-	-	-

The findings of this table are obtained from the Pearson correlation test.

Based on the analysis, chloride level on the first day was correlated with the length of hospital stay in PICU (r=0.26, P= 0.03). No correlation was observed in other cases.

Due to the fact that all patients used only half-normal saline serum (Cl=77meq/L) on hospital days, serum chloride concentration of patients did not change significantly on hospital days, and no case of iatrogenic hypochloremia or hyperchloremia was observed.

Pearson correlation test was used to investigate the relationship between serum chloride levels during three days and the hospital stay, PICU stay, and days of mechanical ventilation (Table 3).

Chloride level on the first day was correlated with the length of hospital stay in PICU (r=0.258,P=0.029). No correlation was observed in other cases.

4- DISCUSSION

Serum chloride abnormalities are common in critically ill patients and appear to be associated with worse patient outcomes (2). The results of this study showed that there was no significant difference between living and deceased people in terms of changes in serum chloride levels during three days. Also, the results showed that there is no significant relationship between serum chloride levels and patients' need for mechanical ventilation in any of the three days. According to the analysis, the chloride level on the first day was correlated with the length of hospital stay in the PICU. This correlation can be considered as an indicator for the outcome of the length of hospital stay in PICU.

Studies have been conducted on the relationship between chlorine and clinical outcomes.

According to a systematic review and meta-analysis (7), although high-chloride fluids did not affect mortality, they were significantly associated with a higher risk of developing acute renal injury and hyperchloremic metabolic acidosis. High-

chloride fluids were also associated with higher serum chloride levels, blood transfusion volume, and duration of mechanical ventilation. According to this meta-analysis, there was a correlation between higher levels of chloride in injected fluids and adverse hospitalization results; however, mortality was not affected by fluid chloride content. The results of this study are consistent with ours on the association between higher chloride and inpatient outcomes.

In a study performed by Stenson et al. (13) on 890 children under the age of 10 who were diagnosed with septic shock, patients' serum chloride levels were recorded for 7 days. In this study, hyperchloremia was considered to be equivalent to a serum chloride concentration greater than or equal to 110 mmol/L. The results indicated that 25% of children developed organ failure and 10% died. A minimum serum chloride greater than or equal to 110 mmol/L was significantly associated with an increased chance of organ failure and mortality. Moreover, the mean serum chloride greater than or equal to 110 mmol/L was significantly associated with mortality. The results of this study indicated that hyperchloremia was independently associated with poorer outcomes in children with septic shock.

The results obtained in the study conducted by Stenson et al. were consistent with those of the present study regarding higher serum chloride concentrations in deceased patients; however, the difference between serum chloride concentration survivors and deceased patients in our study was not significant. Furthermore, in the present study, the relative frequency of deceased patients was higher, compared to the findings of Stenson et al. This difference in the results can be explained by the difference in the definition of hyperchloremia and the number of days of

chloride measurement. It is worth mentioning that the above-mentioned study was conducted on a greater number of patients, compared to the present study.

Barhight et al.(14) performed a retrospective study on a cohort of 1,935 children with a median age of 6.3 years to determine the relationship between mortality and chloride levels at the time of admission or increased chloride levels in children with critical conditions. The death occurred in 4% of children, and acute kidney injury on the second day was observed in 17% of children. Hypochloremia, hyperchloremia, and elevated serum chloride of more than or equal to 5 mEq /L occurred in 2%, 21%, and 12% of children, respectively. It was revealed that an increase in chloride levels on the first day was associated with a 2.3 fold higher chance of death. Elevated serum chloride levels were common during the first day of hospitalization and identified as an independent risk factor for death in critically ill children.

The higher frequency of hyperchloremia, compared to hypochloremia in the study of Barhight et al. was in contradiction with the findings of the present study. This discrepancy may indicate differences in the main findings between the two studies in terms of the effect of chloride content on mortality. Moreover, based on the exclusion criteria, patients who received serums other than 0.5 normal saline were excluded from the present study; therefore, the patients in the present study did not develop iatrogenic hyperchloremia.

The results of two large studies conducted on patients with systemic inflammatory response syndrome showed that mortality was minimal in patients with minimal changes in serum chloride levels. Based on the results, hospital mortality increased per every 10 mmol/L serum chloride increase. This relationship was independent of the total volume of fluids received (15,16).

Measurement of serum chloride for three consecutive days in this prospective study made it possible to study the relationships between the chloride changes in patients and their outcomes. Despite this, it is recommended to conduct simultaneous studies in several centers in longer periods of time, and on with larger sample sizes.

5- CONCLUSIONS

This study showed a correlation between serum chloride levels of children admitted to the PICU and the length of hospital stay. Accordingly, a longer duration of PICU hospitalization was observed in patients with higher serum chloride levels. According to the findings, serum chloride measurement can be considered as an indicator of the length of the patient's hospitalization in the PICU.

5- ETHICAL CONSIDERATIONS

The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.MEDICAL.REC.1397.725).

6- CONFLICT OF INTEREST

None.

7- ACKNOWLEDGMENT

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