Ann Med Res

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Annals of Medical Research

journal page: www.annalsmedres.org

Association of hyperchloremia with acute kidney injury in children with major trauma

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ARTICLE INFO

Keywords:
Acute kidney injury
Hyperchloremia
Major trauma pediatric

Received: Nov 22, 2022
Accepted: Jan 30, 2023
Available Online: 27.02.2023

DOI:
10.5455/annalsmedres.2022.11.347

Abstract

Aim: Hyperchloremia is related to the risks of several morbidities and mortality in seriously sick cases. The effect of hyperchloremia on the incidence of acute kidney injury (AKI) in trauma patients is not well known. Association of hyperchloremia and AKI within the first 72 hour of pediatric intensive care unit (PICU) admission in pediatric trauma patients was investigated.

Materials and Methods: A total of 137 patients with major trauma were investigated retrospectively from tertiary hospital. Serum chloride levels $\geq$ 110 mmol/L described as hyperchloremia. Clinical and laboratory data were compared between AKI and non-AKI. A multivariate logistic regression analysis was used to determine the association between hyperchloremia and AKI.

Results: Totally 109 children were favorable for evaluation following the application of suitability criteria. On admission and at 72 hours, electrolyte measurements were similar between two groups, however chloride level was significantly higher in AKI group (112.33 $\pm$ 4.74 vs. 109.07 $\pm$ 4.90 mmol/L; $p<0.01$) at 72 hours. Ratio of hyperchloremia was remarkably more common in AKI group ($p<0.01$). Hyperchloremia at 72 hours was ensured as an independent risk factor for AKI of pediatric patients with major trauma in the multivariate logistic analysis.

Conclusion: Hyperchloremia frequently seen among major trauma patients adopted to the PICU, and appear to be related to an increased risk for AKI within the first 72 hour of admission.

Introduction

Acute kidney injury (AKI) is a significant prevalent health issue described by increased serum creatinine level and/or reduced urine output because of an abrupt loss of kidney function [1]. Particularly, AKI is independently related to increased probability of progression to end-stage renal disease and increased hospital mortality risk in critically ill patients [2]. Serious trauma initiates primary risk factors of AKI including traumatic inflammation, rhabdomyolysis, hemorrhage, and leads to second crashes due to urgent surgical intervention or inflammations that may induce further kidney disorders resulting in impairment of kidney function [3]. Different type of fluid is used for resuscitation to ensure of perfusion pressure and decreasing the probability of organ failure in trauma patients [4] . In the worldwide, 0.9% sodium chloride fluid referred to as "normal saline" (NS) is the most commonly prescribed intravenous solution for resuscitation [5]. However, the 154 mmol/L chloride concentration in NS is extremely higher than usual 95–105 mmol/L plasma chloride concentration [6]. Therefore, hyperchloremia, determined as plasma chloride concentration above 110 mmol/L, may result from use with large volumes of NS infusion [6]. Recently, the scientific research is interested the probability of injury from hyperchloremia. Several observational investigations have demonstrated increased mortality associated with hyperchloremia and chloride load [7, 8]. Detrimental effect of chloride-rich solutions on renal function have suggested by some human and animal experiments [9, 10]. The relationship between hyperchloremia and kidney injury is explained by vasoconstriction of renal vessel leading to a decrease in perfusion of renal cortical tissue, and renal interstitial edema causing intracapsular hypertension [9, 11]. Defining of AKI risk factors associated with trauma is necessary to prevent probability of AKI and reduce AKI

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associated problems. A past research presenting incidence of AKI after trauma focused either on hemodynamic parameters, medical history, rhabdomyolysis or trauma type as possible risk variables for development of AKI, but there is not enough study was present for focusing on chloride-rich solutions. The main goal of this research was determining the association of hyperchloremia and the development of AKI within 72 hours on admission to pediatric intensive care unit (PICU) in major trauma patients.

Materials and Methods

This retrospective investigation was conducted to examine the association between acute kidney injury and hyperchloremia in pediatric major trauma patients adopted to the tertiary-level university hospital's PICU from February 2020 to August 2022. This research was approved by Afyonkarahisar Health Science University Clinical Research Ethics Committee (2022/8, 2011-KAEK-2). Patients aged 1 month to 18 years old with major trauma who received intravenous fluids with a concentration greater than 0.9% sodium chloride, length of hospital stay $\geq$ 72 hour, and with complete records were enrolled for the study. AKI was described through the Kidney Disease: Improving Global Outcomes 2012 (KDIGO) as an increase in initial serum creatinine (SCr) of 0.3 mg/dl within 48 hours or a 1.5-fold increase in the initial SCr level within seven days or urine output (UOP) of $<$ 0.5 ml/kg/hour for six hours. The exclusion criteria: (1) lack of children baseline records of serum creatinine level; (2) death within 72 hours after PICU admission; (3) children with AKI or missing serum chloride input on PICU admission; (4) children undergoing chronic renal replacement treatment; (5) children with baseline hyperchloremia (chloride $>$ 110 mmol/L); (6) children with an injury severity score (ISS) of less than 15. The total fluid balance was calculated by adding up all the volumes of fluid administered over 72 hours. The fluid management contained both bolus and continuous infusion routes. Pre-PICU fluid management was not included in these data. The sex, age, vital signs on admission (heart rate, mean arterial pressure, and temperature), peripheral oxygen saturation, body surface area (BSA), Glasgow Coma Scale (GCS) score, and characteristics of trauma were collected. The requirement for mechanical ventilation, the period of the intensive care unit, and outcome were recorded. Serum chloride, serum sodium, serum potassium, creatinine, lactate, blood gas, creatine kinase (CK) and coagulation tests were recorded from analysis of blood at admission to the PICU and 72 hours. Delta chloride (Δchloride) was defined as the difference between the chloride level 72-hour post-admission and the baseline level. The highest CK was the maximum value of CK documented during the first 72th hour of PICU stay. Administration of nephrotoxic drugs including aminoglycoside, vancomycin, intravenous contrast agent, and furosemide were included. The clinical severity was evaluated using the Pediatric Risk of Mortality III Score (PRISM III score) and the severity of traumatic injuries was determined using an ISS. Data were obtained from patient records and a hospital electronic info system. Based on a similar research result, with a significance level of α=0.05 and β-1=80%, a minimum required sample size of 20 participants was determined for the study [12].

Statistical analysis

Statistical Package for Social Sciences, version 22 (IBM, Armonk, NY, USA) was used for analyzing of collected data. Descriptive statistics were done for non-parametric quantitative data by the median and interquartile range (IQR), and parametric quantitative data by mean $\pm$ standard deviation, while they were done by frequency and percentage for categorical data. Student's t-test was utilized for analyzing of continuous parameters with normal distribution, while the Mann-Whitney U test was preferred for comparison of non-normally distributed data. The Chi-square test was preferred for evaluation of categorical parameters and Fisher's exact test was preferred when expected cell values were less than 5. Multiple logistic regression analyses were performed for assessing the independent risk parameters for AKI. A value of $p \leq 0.05$ was noticed statistically significant.

Results

One hundred and thirty seven pediatric major trauma patients were enrolled the study. Fifteen patients had an ISS of $<$15, five patients staying in PICU for $<$72 hours, three patients had hyperchloremia or missing serum chloride input at presentation, four children with AKI, and one patient on chronic renal replacement therapy were excluded. After exclusions, 109 patients (60 boys and 49 girls) were eligible for final evaluation. Overall, 79 (72%) survived and 30 (28%) died within 28 days of admission to the PICU. In this population, 21 (19.2%) patients developed acute kidney injury according to the KDIGO criteria. Based on the development of acute kidney injury, the patients were divided into two groups: AKI and non-AKI. The mean age of the AKI group was 88.52 $\pm$ 53.68 months and 9 (42.8%) of patients were female. There were no significant differences between the trauma mechanism; traffic accidents (n: 53, 48.6%) and falls (n: 56, 51.4%), and also no statistically significant difference was encountered between trauma types in terms of survival (p: 0.82). The main characteristic features of major trauma patients are presented in Table 1. There were no considerable differences seen between AKI and non-AKI in terms of respiratory rate, peripheral oxygen saturation, nephrotoxic drugs, BSA, GKS, and PRISM III score. ISS score was higher in patients with AKI (p=0.03). AKI group had lower mean arterial pressure and higher heart rate than non-AKI group (57.05 $\pm$ 14.33 vs. 63.24 $\pm$ 12.10; p: 0.045, 132.62 $\pm$ 24.56 vs. 118.11 $\pm$ 24.49; p=0.016). There wasn't remarkable distinction found between groups in terms of total length of PICU stay and mechanical ventilation day (5 (3.5) vs 6 (4); p=0.24, 5 (2) vs 5 (3); p=0.80). Total infused fluid volume was significantly greater in AKI group (8.3 (2.8) vs. 7.4 (3.2); p=0.04). On PICU admission, there was no patients have hyperchloremia. At the 72nd hour measurements, 30 patients had hyperchloremia. Electrolyte measurements on admission and at 72 hours were similar between two groups, however chloride level was significantly higher in AKI group (112.33 $\pm$ 4.74 vs. 109.07 $\pm$ 4.90 mmol/L; p$<$ 0.01) and also sodium value was higher in AKI group at 72 hours (149.95 $\pm$ 5.76 vs. 143.52 $\pm$ 4.08; p$<$ 0.01). The ratio of AKI was higher in hyperchloremic group than normochloremic group (p$<$0.01). AKI group had obviously

Table 1. Baseline demographic and clinical variables of AKI and non-AKI.

Variables	AKI (n=21)	Non-AKI (n=88)	p value
Age (month), mean ± SD	88.52 ± 53.68	89.10 ± 51.92	0.96
Sex (female n /%, male n/%)	9 (42.8%); 12 (57.2%)	40 (45.4%); 48 (54.6%)	0.63
Respiratory rate (rate/min), mean ± SD	25.67 ± 4.50	25.65 ± 4.23	0.98
Peripheral oxygen saturation, %*	90 (3)	93 (6)	0.10
Heart rate (rate/min), mean ± SD	132.62 ± 24.56	118.11 ± 24.49	0.01
Mean arterial pressure (mmHg), mean ± SD	57.05 ± 14.33	63.24 ± 12.10	0.04
Type of trauma			
Falls	11 (52.3%)	45 (51.1%)	0.82
Traffic accident	10 (47.6%)	43 (48.9%)	
Nephrotoxic drugs (%)			
Aminoglycoside	12.3	11.7	0.16
Vancomycin	28.4	26.8	0.80
Intravenous contrast agent	27.7	28.4	0.14
Furosemide	48.2	46.5	0.21
Duration of mechanical ventilation (day)*	5 (2)	5 (3)	0.80
Duration of PICU (day)*	5 (3.5)	6 (4)	0.24
BSA*	0.73 (0.34)	0.87 (0.33)	0.56
GCS, mean ± SD	8.91 ± 2.69	9.26 ± 3.46	0.12
ISS*	19 (4)	17 (6)	0.03
PRISM III score*	19 (5)	17 (8)	0.07
Total infused fluid volume during 72 h (liter)*	8.3 (2.8)	7.4 (3.2)	0.04

*Median (IQR) PICU: Pediatric intensive care unit; BSA: Body surface area; GCS: Glasgow coma scale; ISS: Injury severity score; PRISM III score: pediatric risk of mortality III score; SD: standard deviation; IQR: interquartile range.

greater delta chloride values (9.52 ± 4.36 vs. 5.60 ± 3.28; p=0.04). The pH levels and base deficit were negligibly different between the groups however, lactate was significantly lower in the AKI group both at admission and at 72 hours (5.59 ± 4.0 vs. 4.0 ± 1.66; p<0.01, 2.3 (2.3) vs. 1.8 (1.45); p=0.01). Hemoglobin level and thrombocyte number was remarkably lower in AKI group (9.8 (4.0) vs 11.40 (2.80); p=0.02, 144 ± 92 vs 231 ± 103; p<0.01). White blood cell count, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and international randomize ratio (INR) were showed resemblance between AKI and non-AKI groups (Table 2). To assess the association between AKI and hyperchloremia the multivariate logistic regression analysis was done by calculating a 95% confidence interval (CI) and odds ratios (OR). For multivariate analysis, the potential predictors defined with bivariate analysis were implicated in the model to determine independent factors for the result. Hyperchloremia at 72 hours is displayed as an independent risk factor for AKI in multivariate analysis, (OR 1.75; 95% CI 1.03-1.98, p= 0.02) (Table 3).

Discussion

Acute kidney injury is a considerable event that seen frequently in hospitalized population. Some evidence points a critical role that even a slight increase in serum creatinine level plays on the outcome of patients [13]. In the last years, there has been an increasing focus on the consequences of resuscitation fluid chloride load and serum chloride in seriously sick patients [14]. Several investigations have shown that chloride-rich crystalloid fluids are associated with increased mortality and/or AKI [15, 16]. In this study, the reliability of using hypertonic saline in terms of renal functions are questioned where it is frequently used in traumatic brain injury. The significances of this study are the cautious preferring of an exemplary pattern of patients with major trauma adopted to the PICU, and the evaluation of the multivariate analysis for clinical confounders directly related to hyperchloremia and AKI like the mean arterial pressure, lactate, total infused fluid volume, and injury severity score. The primary results of this research are as follows. Initially, basic serum electrolyte values of all patients were normal, but hyperchloremia more frequently emerged in AKI group after beginning of therapeutic fluid therapy. Secondarily, analysis of multivariate logistic regression was performed to indicate the other considerable parameters associated with AKI, hyperchloremia was found as an independent risk parameter related to AKI for trauma patients.

The most ordinary reason for development of hyperchloremia in trauma patients after adopted to the intensive care unit is an application of chloride-rich fluids, such as NS and/or HTS [17]. NS is commonly preferred for dilution of medicine and HTS commonly utilized as an osmotic treatment choice to decrease increased cerebral edema might be undetached sources of chloride [18]. The chloride concentration of HTS is 513Eq/L, while that of NS is 154Eq/L, higher than the normal plasma chloride concentration [6]. The relationship between hyperchloremia and AKI has recently caused much controversy in the medical community. In a recent study showed that a lower AKI ratio was seen in intensive care unit patients when limited utilization of chloride-rich fluids [19].

Table 2. Comparison of laboratory findings between AKI and Non-AKI.

Variables	AKI (n=21)	Non-AKI (n=88)	p value
Sodium (mmol/L)			
Initial*	142 (3.75)	141 (2.50)	0.37
At 72 hours, mean ± SD	149.95 ± 5.76	143.52 ± 4.08	<0.01
Potassium (mmol/L)			
Initial, mean ± SD	4.05 ± 0.20	4.04 ± 0.30	0.86
At 72 hours, mean ± SD	3.98 ± 0.50	4.03 ± 0.31	0.34
Chloride (mmol/L)			
Initial, mean ± SD	103.90 ± 3.12	103.27 ± 2.67	0.74
At 72 hours, mean ± SD	112.33 ± 4.74	109.07 ± 4.90	<0.01
Chloride (mmol/L)			
At 72 hours			
<110	7 (33.4%)	72 (81.8%)	<0.01
≥110	14 (66.6%)	16 (18.2%)	
Δchloride (mmol/L), mean ± SD	9.52 ± 4.36	5.60 ± 3.28	0.04
pH			
Initial*	7.34 (0.07)	7.34 (0.07)	0.25
At 72 hours, mean ± SD	7.36 ± 0.04	7.36 ± 0.08	0.99
Base deficit (mmol/L)			
Initial*	1.20 (5.30)	-2.30 (5.70)	0.10
At 72 hours*	1.70 (3.95)	-0.4 (5.05)	0.36
Lactate (mmol/L)			
Initial, mean ± SD	5.59 ± 4.0	4.0 ± 1.66	<0.01
At 72 hours*	2.3 (2.3)	1.8 (1.45)	0.01
Hgb gr/dl *	9.8 (4.0)	11.40 (2.80)	0.02
PLT×10^3/μL, mean ± SD	144 ± 92	231 ± 103	<0.01
WBC×10^3/μL, mean ± SD	16.81 ± 8.35	16.53 ± 5.99	0.85
ALT (U/L)*	63 (82)	56 (69)	0.53
AST (U/L)*	168 (113)	157 (100)	0.41
Albumin g/dL*	3.60 (0.63)	3.59 (0.72)	0.30
INR (U/L), mean ± SD	1.72 ± 0.30	1.68 ± 0.36	0.08
Creatine Kinase (U/L)*	610 (1300) 4	56 (459)	0.28

*Median (IQR) Hgb: Hemoglobin; WBC: White blood cell; PLT: Platelet; INR: international normalized ratio; AST; aspartate aminotransferase; ALT; alanine aminotransferase; SD: standard deviation; IQR: interquartile range.

Table 3. Multivariate Logistic Regression Analysis of AKI vs Non-AKI.

Variables	Odds Ratio	95% Confidence Interval	p value
Total infused fluid volume during 72 h (liter)	0.72	0.68-2.25	0.12
Mean arterial pressure	1.53	1.01-1.72	0.05
ISS score	1.59	1.07-2.14	0.04
Chloride at 72 h	1.75	1.03-1.98	0.02
Lactate on admission	1.24	1.06-1.59	0.08

ISS: Injury severity score.

Current observational research deduced that hyperchloremia within 48 hour of intensive care unit admission was markedly related to AKI and mortality of seriously ill patients [20]. Some observational researches have demonstrated a relation between AKI and chloride-rich solutions. In a large prospective study, it was presented that the incidence of AKI was reduced when the chloride-restricting fluid strategy was applied in the intensive care unit [19]. A current meta-analyzes presented that management of chloride-rich solutions was related to increased risk of hyperchloremic metabolic acidosis and AKI but not death rate [21]. In a different study in cases with septic shock or sepsis found no association between AKI and changes in chloride [14]. Similarly, a recent large randomized trial comparing the effect of buffered crystalloids and 0.9% saline on AKI or mortality showed no significant difference [22]. On the other hand, the Saline against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED) trial comparing saline balanced versus crystalloid in emergency room patients showed a lower incidence of major adverse renal events in the balanced crystalloid group. Particularly, it was reported that the incidence of hyperchloremia (>110 mmol/L) was remarkably lower in the balanced crystalloid group [23].

The relationship between AKI and hyperchloremia is tried to be described with the following hypotheses. Hyperchloremia induced by extended exposure to HTS increases the serum chloride load within renal distal tubule. Persistently increased chloride delivery to the macula densa triggers a signaling cascade that decreases the glomerular filtration rate via 2 basic mechanisms. The first is afferent arteriole vasoconstriction mediated by decreased prostaglandin secretion, and the second is efferent arteriole vasodilation caused by decreased renin and angiotensin II secretion [24]. The combined effect of this prolonged reduced glomerular hydrostatic pressure and renal blood flow leads to decreasing of renal cortical tissue perfusion and tissue ischemia, and feasibly clarifies the relationship observed between persistent hyperchloremia and AKI that is not considered in isolated non-persistent peak chloride values [25].

Conclusion

This retrospective study contributes significantly to the literature in showing that hyperchloremia may have undesirable side effects such as acute kidney injury, particularly for inpatients. After evaluating the results of this study, one may conclude that the regard about the understanding of the efficacy of serum chloride abnormalities on inconvenient outcomes is increasing; there arises to be a relationship between chloride disorders and unsuitable results, in the PICU setting; one could consider they be necessary to more favorable usage of solutions with electrolyte ingredients separate from the physiological solutions; and consider the emergence of hyperchloremia as a prognostic indicator, irrespective of the severity of the disease.

Limitations

There were some limitations to our research. This study has been executed in a single hospital clinic and our comparatively few patients' population may have limited our talent to more understandably illuminate the relationship between acute kidney injury and hyperchloremia. Comorbidity data were not gathered in the study database, with

the exception of chronic kidney disease data, which was systematically noticed as a risk parameter for AKI. Only creatinine criteria were used in the diagnosis of AKI and urine output criteria were not taken into account. We measured level of serum chloride only at admission and 72 hours of the PICU, not at other time intervals of PICU hospitalization. Another limitation is that the analysis of the effect of the fluid type used could not be performed.

Ethics approval

This research was approved by Afyonkarahisar Health Science University Clinical Research Ethics Committee (2022/8, 2011-KAEK-2).

Authorship contributions

Concept: M.Ç., K.Ç.; Design: M.Ç., K.Ç; Supervision: K.Ç; Data: M.Ç.; Analysis: K.Ç, M.Ç.; Literature search: K.Ç.; Writing: K.Ç.; Critical revision: K.Ç.

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