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Research Article

Hyperchloremia and Its Association with Outcomes in Critically Ill Children

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Abstract

To determine the relationship of hyperchloremia on development of Acute Kidney Injury (AKI), hyperchloremic metabolic acidosis, PICU length of stay and mortality in critically ill children. We did retrospective review of medical records of all children (aged 1 month to 16 years) admitted in our PICU from January to December 2015. Study population was divided into groups based on Chloride (Cl) level. Children with Cl level >110 meq/L were labelled as hyperchloremic groups and those with <110 as normochloremic group. Patients having acute kidney injury on admission and length of PICU stay <24 hours were excluded. A total 200 patients were identified, 100 in each group. Mean age was 55.59 ± 57.77 months with no difference between the two groups (p 0.66). 63% were males. Mechanical ventilation was needed in 50% patients, inotropes in 21.6 and renal replacement therapy in 14%. There was no significant difference between the two groups in development of AKI, length of PICU stay or survival (p value >0.05).

Background

Parenteral fluid therapy is the second most important therapeutic intervention in critically ill children [1]. Isotonic saline (normal saline, NS) has been the traditional fluid of choice for resuscitation for last more than a decade [2,3]. But NS has been termed as neither normal nor physiological because of increasing awareness of its association with hyperchloremic metabolic acidosis [4]. Previously hyperchloremia was thought to be benign but now it has been shown to be associated with acidosis and other adverse dysfunction including Acute Kidney Injury (AKI) due to intense renal vasoconstriction, gut dysfunction and immune dysregulation [5]. Hyperchloremia is thought to affect the release of eicosanoid in renal tissue, which leads to vasoconstriction and resultant glomerular filtration rate reduction [6]. Several observational studies in adults as well as pediatric population have demonstrated isotonic saline (high chloride) used either as a resuscitation fluid or maintenance fluid causes not only hyperchloremic metabolic acidosis but also higher incidence of acute kidney injury, prolonged hospital stay and higher mortality rate as compared to low chloride solutions [7-11].

Similar data on hyperchloremia in children and it adverse effects in critically ill children are limited specially a developing country like Pakistan. We aim to determine the effects of hyperchloremia on outcome in a diverse group of critically ill children admitted in our multi-disciplinary Pediatric Intensive Care Unit (PICU)

Objective

To determine the effects of Hyperchloremia in critically ill children by comparing Normochloremic patients with hyperchloremic patients. These effects included metabolic acidosis, development of AKI, PICU length of stay and mortality.

Materials and Methods

This retrospective cohort study was done at our tertiary care, multi-disciplinary, 4 bedded PICU after approval from hospital ethical review committee (3521-Ped-AKU-15). All children aged 1 month to 16 years old admitted in PICU from January 2015 to December 2015 and had a PICU Length of Stay (LOS) more than 48 hours were included. Patients who had Acute Kidney Injury (AKI) on admission and patients having length of stay <48 hours were excluded. Hyperchloremia was defined as serum Chloride (Cl) levels >110 meq/L on admission to PICU that persisted for the first 24 hours of admission [11]. A second Cl levels were also taken into consideration at 24 hours of admission to PICU. Study population was divided into two groups based on chloride levels during the first 24 hours; one with normal chloride levels and other with high chloride levels. Patients with first Cl levels >110 meq/L and second level <110meq/L were excluded from the study. The highest Cl levels were taken for analysis purpose. These groups were then compared with respect to development of AKI, Hyperchloremic Metabolic Acidosis (HCMA), PICU LOS and mortality. AKI was defined as per modified pRIFLE criteria [12]. For the calculation of base deficit and anion gap we used the modified steward equation similar to that used by O' Dell et al [10].

All the patients in our PICU and emergency room with shock (septic or others) are managed with isotonic saline boluses initially as per PALS guidelines and NS with 5% dextrose is used as maintenance fluid therapy. Hypertonic saline therapy is provided to patients with any acute neurological disorder on physician discretion as well as to patients with symptomatic hyponatremia.

Data was collected on a structured form and included basic demographic details (age, gender), diagnostic category, PICU interventions (mechanical ventilation, renal replacement therapy and inotropic support), laboratory variables (electrolytes, blood gas values, creatinine, blood urea nitrogen) and outcome variables (PICU length of stay, development of AKI, development of hyperchloremic metabolic acidosis and mortality). Highest recorded values were taken for analysis purpose.

Data was analyzed using SPSS version 20. Results are presented as mean with standard deviation and frequency with percentage for continuous and categorical variables respectively. Chi-square test was used for comparison of two groups for categorical variables and Student t test were used for comparison of continuous variables between two groups. The association of Hyperchloremia with outcome variables (AKI, PICU LOS, mortality) was further tested by multivariate logistic regression models. P value, Odd ratios with 95% confidence interval is reported. Receiver Operative Curve (ROC) was generated for chloride levels for the development of HCMA, AKI and survival.

Results

A total of 340 patients were admitted in PICU during the study period, 200 met the inclusion criteria and were included in the study. Mean age of the study population was 55.6 ± 57.8 months (53.8 ± 59.1 months in normochloremic group and 57.4 ± 56.7 months in hyperchloremic group) and 126 (63%) were males (Table 1).

Table 1: Comparison of demographic, clinical and outcome characteristics of between Normochloremic and Hyperchloremic critically ill children.

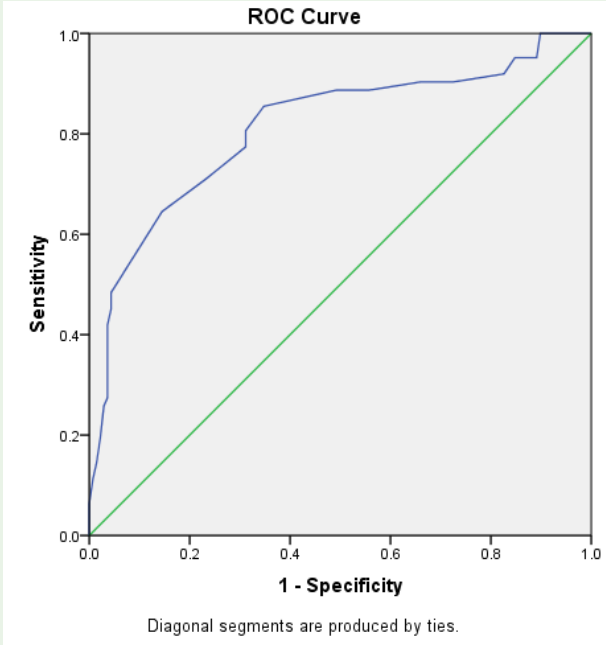
Variable	Overall N=200 (%)	Normochloremia (n=100)	Hyperchloremia (n=100)	OR (95%CI)	p-value (<0.05 sig.)
Age in Months (Mean ± Standard Deviation)	55.59 ± 57.77	53.82 ± 59.10	57.37 ± 56.66	-12.59 – 19.66	0.665
Gender Male N (percentage)	126 (63)	65 (65)	61 (61)	0.84 (0.47 – 1.50)	0.558
Diagnostic Category					
CNS	44 (22)	20 (20)	24 (24)	1.5 (0.677 - 3.334)	0.35
CVS	50 (25)	27 (27)	23 (23)	1.739 (0.977-3.093)	0.77
Respiratory	30 (15)	13 (13)	17 (17)	0.26 (0.108 – 0.658)	0.79
Sepsis/Shock	16 (8)	6 (6)	10 (10)	1.179 (0.382- 3.641)	0.30
Post-Surgical	20 (10)	13 (13)	7 (7)	1.762 (0.959 – 3.23)	0.66
Miscellaneous	40 (20)	21 (21)	19 (19)	0.658 (0.360 – 1.200)	0.10
Interventions					
Mechanical Ventilation	101 (50.5)	59	42	0.478 (0.199-1.145)	0.098
Inotropic Support	43 (21.5)	22	21	1.148 (0.377-3.501)	0.49
Renal Replacement Therapy	28 (14)	16	12	1.111 (0.247-4.996)	0.48
Hypertonic Saline	15 (7.5)	8	7	2.227 (0.307-16.131)	0.428
Labs					
Chloride Levels	110.17 ± 10.76	101.68 ± 6.61	118.66 ± 6.58	15.13 - 18.82	<0.01
AG (Mean with Standard Error)	12.57 (0.577)	12.49 (0.969)	12.65 (0.631)	1.003 (0.945-1.064)	0.927
Serum Creatinine (Mean with Standard Error)	0.64 (0.047)	0.65 (0.074)	0.63 (0.056)	0.638 (0.169-2.409)	0.507
Creatinine Clearance	129.5 (95.6)	115.1 ± 93.10	143.9 ± 96.4	2.29 - 55.16	0.033
Outcomes					
LOS PICU (Mean ± SD)	6.81 (+5.02)	7.27 (+5.99)	6.34 (±3.79)	1.00 (-2.33- 0.47)	0.09
HCMA	62 (31)	17	45	1.145 (0.361-3.631)	0.818
AKI	70 (35)	42	28	0.567 (0.092-3.485)	0.540
Discharge Disposition (Expired)	30 (15)	18	13	1.47 (0.67 ± 3.18)	0.43

CNS: Central Nervous System, CVS: Cardiovascular System, AG: Anion Gap, LOS: length of Stay, HCMA: Hyperchloremic Metabolic Acidosis, AKI: Acute Kidney Injury.

Table 2: Independent Risk Factors for outcome (multivariate logistic regression).

Outcome: Mortality (n=30)			
Variables	**Hazard Ratio**	**95% Confidence Interval**	**P value**
Hyperchloremia	0.80	0.38 – 1.65	0.55
Inotropic Support	3.50	1.70 – 7.21	<0.05
Age (Months)	0.98	0.98 – 0.99	0.02
Outcome: Acute Kidney Injury (n= 85)			
Hyperchloremia	0.79	0.51 – 1.22	0.29
Age (Months)	0.99	0.98 – 0.99	<0.05
Outcome: Length of Stay			
Hyperchloremia	-0.16	-1.69 – 1.36	0.83
Fluid Overload	6.55	2.53 – 10.57	0.002
Hypertonic Saline	3.82	3.89 – 6.12	0.01

Major diagnostic categories included cardiovascular diseases (50, 25%), neurological diseases (44, 22%), respiratory diseases (30, 15%), sepsis/septic shock (16, 8%), while 20 (10%) were admitted for post-operative care and rest had miscellaneous diagnosis. 63 (31.5%) patients received mechanical ventilation in PICU, 43 (21.5%) required inotropic support and 15 (7.5) received hypertonic saline in their therapy while 28(14%) required renal replacement therapy during their PICU stay.



Area Under the Curve				
Test Result Variable(s): CI				
Area	Std. Error[a]	Asymptotic Sig[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.811	.036	.000	.741	.882
The test result variable(s): CI has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.				
a. Under the nonparametric assumption				
b. Null hypothesis: true area = 0.5				

Figure 1: Receiver Operative Curve for Chloride levels on Hyperchloremic Metabolic Acidosis.

Mean chloride levels at admission were 110.1 ± 10.76 meq/L (118.66 ± 6.58 in hyperchloremic group and 101.68 ± 6.61 in Normochloremic group, p= <0.01). While mean Cl levels at 24 hours of admission were 112 ± 9.21 meq/L (120.20 ±5.78 in hyperchloremic group and 102.33 ± 7.71 in Normochloremic group, p= <0.01. Mean Sodium (Na) levels were 140.9 ± 6.4 meq/L (143 ± 5.0 in hyperchloremic group and 137.9 ± 6.3 in Normochloremic group, p= <0.01). Mean bicarbonate (HCO3) levels were 20.54 ± 6.02 meq/L (20.43 ± 6.15 in hyperchloremic group and 20.66 ± 5.92 in Normochloremic group, p= <0.78). Mean (Mean AG level was 12.57 ± 8.1 (12.6 ± 6.3 in hyperchloremic group and 12.5 ± 9.7 in normochloremic group) (p=0.577). HCMA developed in 62 patients (31%), 45 (45%) patients in Hyperchloremia group and 17 patients (17%) in normochloremia group (p <0.05) Mean Serum Creatinine levels were 0.64 ± 0.65 mg/dl (0.63 ± 56 mg/dl in hyperchloremic group and 0.65 ± 0.73 mg/dl in normochloremic group). Creatinine clearance by Schwartz formula was 143.9 ± 96.44 in hyperchloremic group and 115.1 ± 93.1 in normochloremic group. Mean length of PICU stay was 5.48 ± 0.398 days (7.27+5.99 days in normochloremic group and 6.34 ± 3.79 days in hyperchloremic group), and 85 (42.5%) patients developed AKI during their PICU stay (Table 1).

On Univariate analysis younger age, use of inotropic score and fluid overload were associated with mortality (p= 0.05). Similarly fluid overload, use of hypertonic saline and inotropic support, mechanical ventilation and renal replacement therapy were associated with prolonged hospital length of stay (p <0.05). On multivariate logistic regression analysis younger age was associated with increased mortality and development of AKI while fluid overload was associated with prolonged hospital length of stay (Table 2).

Receiver Operator Curve (ROC) for the prediction of hyperchloremia for AKI, HCMA, and survival were 0.53, 0.81, and 0.54, respectively (Figure 1).

Discussion

In our study we didn't find a statistical significant association of hyperchloremia with development of AKI, LOS and mortality. Development of HCMA was significant in hyperchloremic group as compared to normochloremia group. On ROC analysis chloride levels of >106.5 meq/L showed a sensitivity of 77.4% and specificity of 69% for development of hyperchloremia. Various previous studies and reviews have highlighted the development of hyperchloremia and its effects on various body systems specially development of AKI [4]. In a previous study by Hatherill et al. in children following open cardiac surgery showed that hyperchloremia was present in 70% of their patients but this hyperchloremia was not associated with increased mortality or increased length of stay which is similar to our findings [3]. Instead it was associated with decreased mortality. We found no mortality difference between hyperchloremic group and normochloremic group. Similarly another study by O' Dell et al showed significant development of HCMA in the post resuscitation phase of pediatric meningococcal sepsis but they didn't look at the association of HCMA with outcome [10]. On the other hand Yunos et al. in a prospective open label trial showed that chloride liberal intravenous fluid therapy was significantly associated with development of AKI and need for RRT [9]. While we didn't find any statistically significant difference on the need for inotropic support, development of AKI and need for RRT. It is also important to differentiate lactic acidosis from

post resuscitation HCMA in critically ill children. As lactic acidosis and hyperlactatemia are associated with high PICU mortality while hyperchloremia is result of isotonic fluid resuscitation [14,15]. So this debate of isotonic versus balanced salt solution in critically ill children continued [8] and till we have a final answer we should continue the use of isotonic saline for resuscitation as well as maintenance fluid therapy in critically ill children while carefully looking for the development of hyperchloremia. The safety of HCMA in diverse critical disease spectrum has not been prospectively and systematically studied. We didn't find any difference on development of hyperchloremia or its adverse effects based on their primary disease categories or individual diseases. Out patient population had a very wide spectrum of disease and probably the major diseases number is still small to draw a statistical conclusion about the development of hyperchloremia in specific diseases and its adverse outcomes. But being iatrogenic in most cases, HCMA should be avoided whenever possible.

Strengths and Limitation

We have many limitations in our study including a retrospective, single center study with limited sample size and uncontrolled data. This could limit the generalizability of the results. So a prospective cohort study or a matched case control study will be better design to further answer these questions.

But never the less we feel that it is a good comparison of the two groups with diverse spectrum of underlying disease process and it paves the way for further clinical trials in this area in critically ill children.

Conclusion

We didn't find any difference in outcome between hyperchloremia and normochloremia.

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