Blood chloride levels in children given 0.9% normal saline as fluid for resuscitation followed by isotonic maintenance fluid

***Kumar Gaurav[1], B M John[2], Sandeep Dhingra[3]**

Sri Lanka Journal of Child Health, 2022; **51**(3): 385-390
DOI: http://dx.doi.org/10.4038/sljch.v51i3.10237

Abstract

Background: In the last few years there have been several studies describing the occurrence of hyperchloraemia following the use of isotonic fluids. These studies have shown variable results with respect to its prevalence and outcomes. Studies in the paediatric population have been sparse.

Objectives: To study the prevalence of hyperchloraemia in the first 48 hours in children who received 0.9% normal saline as fluid for resuscitation and to assess the relationship of hyperchloraemia with outcomes such as use of inotropes, acute kidney injury (AKI), length of stay and mortality.

Method: A cross-sectional study was conducted in the department of paediatrics of a tertiary care hospital; 118 children who were admitted in the paediatric intensive care unit / high dependency unit were enrolled in the study. Blood chloride levels were checked at 0-6 hours, 12-24 hours and 24-48 hours. Data analysis was done using SPSS software version 16 and Microsoft Excel 2007.

Results: Mean age of the sample population was 5.45 ± 3.97 years with 52% of them being boys; 22.9% children developed hyperchloraemia. There were significant differences in chloride levels between the hyperchloraemia and normochloraemia groups at all three-time frames (p=0.000). The chloride levels started to rise after 6 hours of normal saline bolus and continued to show a rising trend with the highest values at 48 hours. The sodium levels at various time points were all within the normal range. Presence of hyperchloraemia was associated with acute kidney injury (AKI) in the study population (p=0.040). However, hyperchloraemia was not associated with the need of inotropes (p=0.058), length of stay (p=0.499) or mortality (p=0.302).

Conclusions: Hyperchloraemia was seen in 22.9% of the study population and there was a significant association with AKI but not with the need of inotropes, length of stay or mortality.

(Keywords: Normal saline, Hyperchloraemia, Outcomes)

[1]*Junior Resident,* [2]*Professor, Department of Paediatrics, Armed Forces Medical College, Pune, India,* [3]*Professor, Department of Paediatrics, Command Hospital (Western Command), Chandimandir, Haryana, India*
**Correspondence:* drkumargaurav8@gmail.com
https//orcid.org/0000-0002-2686-3061

(Received on 17 December 2021: Accepted after revision on 18 February 2022)
The authors declare that there are no conflicts of interest
Personal funding was used for the project.

Introduction

In hyperchloraemia there is elevation of chloride ions more than 110mEq/L[1-5]. Mechanisms leading to the development of hyperchloraemia include excessive chloride administration, water loss in excess of chloride loss and increased renal reabsorption of chloride[6]. Whilst persons with hyperchloraemia secondary to chloride free fluid losses will show signs of dehydration, persons with hyperchloraemia secondary to administration of normal saline will show signs of an expanded extracellular fluid volume[7]. Normal saline (NS) contains supra-physiological levels of chloride (154mEq/L). The chloride content varies with the composition of different fluids. Hyperchloraemia predisposes to non-anion gap metabolic acidosis which may result in an adverse outcome[2,3]. Studies have shown the development of acute kidney injury (AKI) in association with hyperchloraemia[2,5,8]. Poor outcomes have been noted with use of chloride-rich fluids in patient with diabetic ketoacidosis[9,10] and septic shock[11]. Studies in children on this topic are scanty.

Objectives

To study the prevalence of hyperchloraemia in the first 48 hours in children who received 0.9% normal saline as fluid for resuscitation and to assess the relationship of hyperchloraemia with outcomes such as use of inotropes, AKI, length of stay and mortality.

Method

A prospective cross-sectional study was conducted in the Department of Paediatrics of a tertiary care teaching hospital in western India over a period of 18 months from October 2018 to March 2020. Hyperchloraemia was defined with serum values more than 110mEq/L. All children aged 1-14 years, admitted in the paediatric intensive care unit (PICU) or high dependency unit (HDU), who received at least 20ml/kg or more NS in the first 6 hours of admission were eligible to participate in the study. Children who had a history of resuscitation prior to admission or received fluid therapy other than NS and children who were diagnosed as AKI within 6 hours of admission were excluded from the study. AKI was defined using Kidney Disease Improving Global Outcomes (KDIGO) criteria using the serum creatinine values[12].

Sample size: Prevalence of hyperchloraemia was 16.6% (p = 16.6) as per Tani M, *et al*[3] study

So q = 100 - p = 100 – 16.6 = 83.4

$N = Z^2 p q / L^2$

$N = \frac{(1.96)^2 \times 16.6 \times 83.4}{10 \times 10}$ N = 53.18

Thus, the minimum sample size required to conduct the study was approximately 53. We kept on enrolling the subsequent children who met the inclusion criteria. According to the inclusion criteria all children who received 20ml/kg of NS bolus over 1 hour and were having signs of shock with poor perfusion, capillary filling time (CFT) >3 seconds and cold peripheries, irrespective of the blood pressure, i.e., both compensated and hypotensive shock, were included in the study. There were 118 children during the 18 months of study who met the inclusion criteria and were enrolled. Sampling unit was 'individual'. Convenient sampling technique was used.

Data on baseline characteristics and other relevant data were obtained from the parental history and case records. Data were recorded in a predesigned format. Blood values of sodium were analysed to see the sodium profile at different point intervals. Venous / arterial blood samples for sodium, chloride, partial pressure of carbon dioxide (pCO_2), pH and bicarbonate were taken. The serum values of sodium and chloride were sent to the laboratory as per discretion of the treating physician. Initial normal saline resuscitation (20ml/kg) was started in all children based on unit protocol; 0.9% dextrose normal saline (DNS) was used as maintenance fluid. Patients were subjected to investigations after NS bolus to assess blood chloride levels at 0-6 hours, 12-24 hours and 24-48 hours. Other routine investigations were sent at the discretion of the treating physician.

Ethical issues: The study was approved by the Institutional Ethics Committee of the Armed Forces Medical College, Pune, India (Ref. No. EC/Oct/2018). Written informed consent was obtained from the parents of the participating children.

Statistical analysis: Data were analysed using SPSS software version 16 and Microsoft Excel 2007. Chi-square test with Yates' correction was used to compare categorical variables; the unpaired t-test was used to compare normally distributed continuous variables between the groups. Regression analysis was used for estimating the relationship between dependent and independent variables. A value of two tailed $p < 0.05$ was considered significant.

Results

The study population consisted of 118 children with a mean age of 5.45 ± 3.97 years with a range of 1 to 16 years. There were 61 (52%) males. There were 68 (57.6%) children in the ≤ 5-year age group, 35 (29.7%) in the 6-10 year age group and 15 (12.7%) in the >10 years age group. The study population included 41 with acute gastroenteritis, 40 with shock (sepsis, dengue shock syndrome, nephrotic syndrome with hypovolaemia) and 37 with miscellaneous causes. Underlying co-morbidities were found in 44 (37.3%) children. Haematological conditions were found in 23 cases and included acute myeloblastic leukaemia, acute lymphoblastic leukaemia and sickle cell anaemia. Central nervous system (CNS) conditions included head injury, status epilepticus, arginaemia, organic acidaemia, craniosynostosis and developmental delay. Twenty-seven (22.9%) children developed hyperchloraemia following NS infusion among the study population. The profile of mean blood chloride levels in the hyperchloraemic and normochloraemic groups are shown in Table 1.

Table 1: ***Profile of mean blood chloride levels in the hyperchloraemic and normochloraemic groups***

Blood chloride - time frame	Hyperchloraemia	Number	Mean ± SD	SE	p-value
0-6 hours	Present	27	107.92 ± 3.93meq/L	0.76	0.000
	Absent	91	100.8 ± 2.90meq/L	0.30	
12-24 hours	Present	27	111.6 ± 5.54meq/L	1.07	0.000
	Absent	91	101.85±2.14meq/L	0.22	
24-48 hours	Present	27	114.31 ± 6.33meq/L	1.22	0.000
	Absent	91	102.92 ± 2.35meq/L	0.25	

The mean blood chloride levels started to rise after 6 hours of 0.9% bolus and showed an increasing trend during the serial measurement in both the normochloraemic and hyperchloraemic groups (Figure 1).

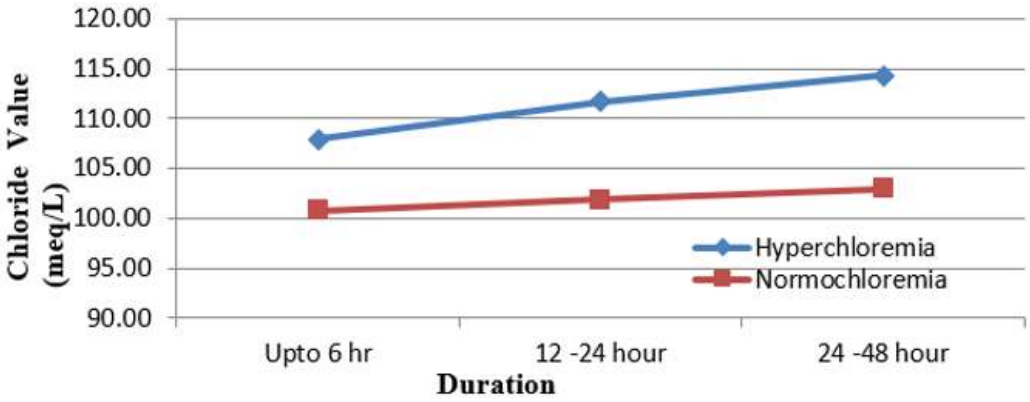

Figure 1: ***Line diagram of chloride levels in both groups***

On receiver operating characteristic (ROC) analysis, chloride levels of >104.6meq/L showed a sensitivity of 100% and specificity 91.2% for development of hyperchloraemia. The blood sodium levels at various time points were all within the normal range (Figure 2).

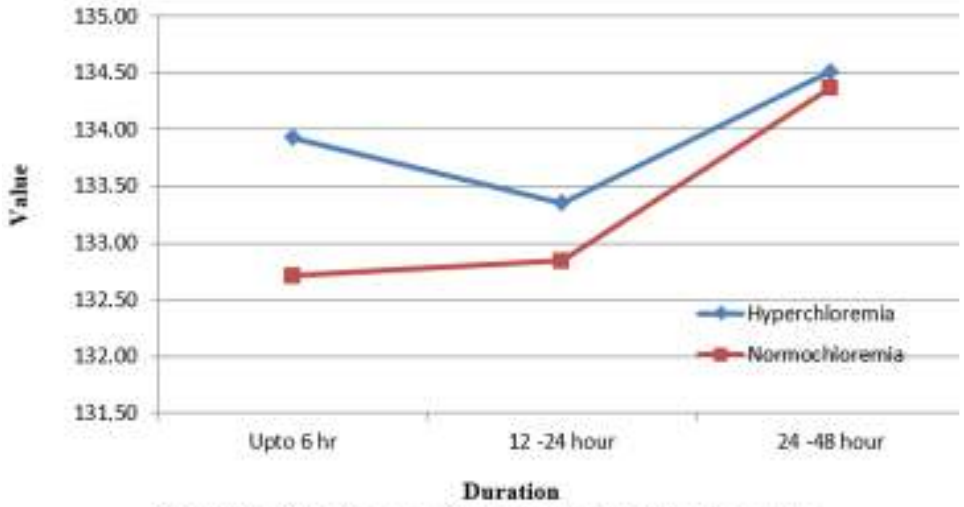

Figure 2: ***Line diagram of sodium levels in both groups***

On application of unpaired t-test there was no significant difference in blood sodium levels between the hyperchloraemic and normochloraemic group. There was a significant association of hyperchloraemia with AKI (Pearson Chi-Square 1.091; p =0.040) (Table 2).

Table 2: ***Comparison of outcome between the groups***

Outcome	Hyperchloraemia *(n=27)* n (%)	Normochloraemia *(n=91)* n (%)	Total n (%)	p-value
Acute kidney injury	06 (22.2)	06 (06.6)	12 (10.2)	0.040*
Mortality	05 (18.5)	10 (11.0)	15 (12.7)	0.302
Inotropes	06 (22.2)	08 (08.8)	14 (11.9)	0.058

* *p<0.05*

However, no association was seen with the need for inotropes (Pearson Chi-Square 3.59; p=0.058), length of stay (p=0.499) and the mortality (Pearson Chi-Square 1.064; p=0.302) though the mean duration of hospital stay in hyperchloraemia children (8.89 days) was higher than those without hyperchloraemia (7.96 days). We also did not find any significant association of prevalence of hyperchloraemia in children with or without underlying co-morbidities.

Discussion

The choice of intravenous fluid recommended in children has been the subject of intense debate over the last few years[12]. This has undergone a change from hypotonic fluid to isotonic maintenance fluids to avoid symptomatic hyponatraemia[13]. However, the use of isotonic fluids such as 0.9% NS has the potential to give rise to hyperchloraemia[2,3,4]. We analysed 118 children admitted in PICU/HDU who received at least 20ml/kg of 0.9% NS bolus during resuscitation in the first 6 hours of admission followed by maintenance fluid based on unit protocol; 22.9% children developed hyperchloraemia. The chloride levels started to rise after 6 hours of NS bolus and continued to show the rising trend with highest values at 48 hours. The various studies in the past have shown a prevalence of hyperchloraemia from 16.6 to 94.9% in children[2-5,11-13].

We found an association of hyperchloraemia with AKI (Pearson Chi-Square 1.091; p= 0.040). However, there was no association with use of inotropes, length of stay or mortality. Past studies have shown hyperchloraemia to be associated with several adverse outcomes such as hyperchloraemic metabolic acidosis[2] and AKI[3,11,14]. Hyperchloraemia, in many clinical settings, has been hypothesised to cause renal hypoperfusion and AKI by virtue of its renal vascular smooth muscle constrictor effect[15,16]. Bulfon A, *et al*[2], in their Hyperchloraemia in Critically Ill Paediatric (HYCIP) study had an incidence of 94.9% hyperchloraemia in a total of 541 patients. Tani M, *et al*[3]. in their study of 488 patients above 16 years who stayed more than 48 hours inside the PICU, found hyperchloraemia in 81 (16.6%) children. Stenson EK, *et al*[4] studied 890 children aged less than 10 years with severe sepsis or septic shock. A chloride level more than 110meq/L was associated with increased odds of complicated course (OR 1.9, 95% CI 1.1 – 3.2, p = 0.023) and mortality (OR 3.7, 95% CI 2.0 – 6.8, p <0.001). Suetrong B, *et al*[11], in his study of 240 patients, found that 98 (40.8%) patients above 18 years had hyperchloraemia within the first 48 hours of resuscitation. Barhight MF, *et al*[5] in their large study of 1935 critically ill children found that an increase in chloride ≥ 5mEq/L was associated with a 2.3 (95% CI: 1.03-5.21) greater odds of mortality. Chua HR, *et al*[9] compared Plasma-Lyte 148 vs. 0.9% saline for fluid resuscitation in diabetic ketoacidosis (DKA) and found that serum chloride levels were higher in NS administered groups compared to Plasma-Lyte administered group.

Baalaaji M, *et al*[10] evaluated 79 patients of DKA out of which 28 children had AKI. On multivariate analysis, elevated chloride levels at 24 hours had an independent association with AKI progression [Adjusted OR 1.14 (95% CI 1.04-1.27); p=0.007]. Krajewski ML, *et al*[12] reviewed 21 studies with a total of 6253 patients. In their study they evaluated patients who had received high chloride intravenous fluids in the peri-operative or ICU care setting. They inferred that high-chloride fluids did not affect mortality but were associated with a significantly higher risk of AKI (RR 1.64; 95% CI 1.27 to 2.13; p<0.001) and hyperchloraemic metabolic acidosis (RR 2.87; 95% CI 1.95 to 4.21; p < 0.001). Bulfon A, *et al*[2] in their study in 2019 found that hyperchloraemic metabolic acidosis was not associated with an increased risk of AKI. All these multiple studies have shown varying prevalence of hyperchloraemia in different subsets of population. The adverse outcome profiles with hyperchloraemia have also been inconsistent except for occurrence of AKI.

There were certain limitations to our study. Our sample size was small with a mixed population of children with various underlying aetiologies. We did not consider the baseline blood gas and electrolytes which should have been analysed before NS bolus. We should have looked at anion gap on follow up and kept a record of amount, type and duration of maintenance fluids. Hence, we recommend studies with a larger sample size across various disease conditions to validate our findings.

Conclusions

In the study subjects 22.9% developed hyperchloraemia. The chloride levels first measured close to 6 hours were high and continued to rise with maximum values at 48 hours. We found a statistically significant association of hyperchloraemia with AKI. However, there were no significant associations with other studied outcomes like use of inotropes, length of stay or mortality.

References

1. Morrison G. Serum chloride. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths; 1990.

2. Bulfon A, Stef S, Alomani H, Comrie B, Vanniyasingam T, Zheng K, *et al*. Hyperchloraemia in critically ill paediatric patients. The "HYCCIP" study. *Pediatric Critical Care Medicine* 2018; **19**(6S): 146. https://doi.org/10.1097/01.pcc.0000537783.94346.55

3. Tani M, Morimatsu H, Takatsu F, Morita K. The incidence and prognostic value of hypochloraemia in critically ill patients. *Scientific World Journal* 2012; **2012**: Article ID 474185. https://doi.org/10.1100/2012/474185 PMid: 22701359 PMCid: PMC3373177

4. Stenson EK, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, Bigham MT, *et al*. (2018). Hyperchloraemia is associated with complicated course and mortality in paediatric patients with septic shock. *Pediatric Critical Care Medicine*; **19**(2): 155-60. https://doi.org/10.1097/PCC.0000000000001401 PMid: 29394222 PMCid: PMC5798001

5. Barhight MF, Brinton J, Stidham T, Sorano DE, Faubel S, Griffin BR, *et al.* Increase in chloride from baseline is independently associated with mortality in critically ill children. *Intensive Care Medicine* 2018; **44**(12): 2183-91. https://doi.org/10.1007/s00134-018-5424-1 PMid: 30382307

6. Bandak G, Kashani KB. Chloride in intensive care units: a key electrolyte. *F1000 Research* 2017; **6**: 1930. https://doi.org/10.12688/f1000research.11401.1 PMid: 29123653 PMCid: PMC5668919

7. Gunnerson KJ. Clinical review: The meaning of acid–base abnormalities in the intensive care unit part I–epidemiology. *Critical Care* 2005; **9**(5): 508. https://doi.org/10.1186/cc3796 PMid: 16277740 PMCid: PMC1297622

8. Yunos NM, Bellomo R, Story D, Kellum J. Bench-to-bedside review: Chloride in critical illness. *Critical Care* 2010; **14**(4): 226. https://doi.org/10.1186/ https://doi.org/10.1186/cc9052 PMid: 20663180 PMCid: PMC2945073

9. Chua HR, Venkatesh B, Stachowski E, Perkins K, Ladanyi S, Kruger P, et al. Plasma-Lyte 148 vs 0.9% saline for fluid resuscitation in diabetic ketoacidosis. *Journal of Critical Care* 2012; **27**(2):138-45. https://doi.org/10.1016/j.jcrc.2012.01.007 PMid: 22440386

10. Baalaaji M, Jayashree M, Nallasamy K, Singhi S, Bansal A. Predictors and outcome of acute kidney injury in children with diabetic ketoacidosis. *Indian Pediatrics* 2018; **55**(4): 311-4. https://doi.org/10.1007/s13312-018-1274-8 PMid: 29428918

11. Suetrong B, Pisitsak C, Boyd JH, Russell JA, Walley KR. Hyperchloraemia and moderate increase in serum chloride are associated with acute kidney injury in severe sepsis and septic shock patients. *Critical Care* 2016; **20**(1): 315. https://doi.org/10.1186/s13054-016-1499-7 PMid: 27716310 PMCid: PMC5053142

12. Krajewski ML, Raghunathan K, Paluszkiewicz SM, Schermer CR, Shaw AD. Meta-analysis of high- versus low-chloride content in perioperative and critical care fluid resuscitation. *British Journal of Surgery* 2015; **102**(1): 24-36. doi:10.1002/bjs.9651 https://doi.org/10.1002/bjs.9651 PMid: 25357011 PMCid: PMC4282059

13. Bulfon AF, Alomani HL, Anton N, et al. Intravenous fluid prescription practices in critically ill children: A shift in focus from natraemia to chloraemia? *Journal of Pediatric Intensive Care* 2019; **8**(4): 218-25. https://doi.org/10.1055/s-0039-1692413 PMid: 31673457 PMCid: PMC6821529

14. Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in

critically ill adults. *JAMA* 2012; **308**(15): 1566-72.
https://doi.org/10.1001/jama.2012.13356
PMid: 23073953

15. Marttinen M, Wilkman E, Petäjä L, Suojaranta-Ylinen R, Pettilä V, Vaara ST. Association of plasma chloride values with acute kidney injury in the critically ill–a prospective observational study. *Acta Anaesthesiologica Scandinavica* 2016; **60**(6): 790-9..
https://doi.org/10.1111/aas.12694
PMid: 26866628

16. Zhang Z, Xu X, Fan H, Li D, Deng H. Higher serum chloride concentrations are associated with acute kidney injury in unselected critically ill patients. *BMC Nephrology* 2013; **14**(1): 235. DOI:org/10.1186/1471-2369-14-235.
https://doi.org/10.1186/1471-2369-14-235
PMid: 24164963 PMCid: PMC4231437