Research Article

Hyperchloremia and mortality in the ICU: a prospective cohort study

Abstract

Introduction: Part of the interventions in patients admitted to intensive care units (ICU) consist of the administration of crystalloids, implying a risk for the development of side effects. One of these is hyperchloremia, linked to the appearance of metabolic acidemia and systemic inflammatory response. Given these findings, observational studies have been developed, trying to establish an association between hyperchloremia and outcomes such as mortality and kidney failure; however, its diverse results prompt the development of new studies. In Colombia, there are no prospective cohort studies that establish any type of association with hard outcomes. Goal. To determine the association between the development of hyperchloremia and mortality and acute renal failure, in patients hospitalized in the ICU, in two hospitals in Bogotá D.C.

Methodology: Analytical prospective cohort study conducted between June 1, 2019 and August 31, 2021.

Results: 325 patients were analyzed, the cumulative incidence of hyperchloremia and acute renal failure in the entire study population was 44.6% and 29.5%, respectively. The cumulative incidence of death in the exposed was 36.5% vs 23.3% in the unexposed, with a relative risk RR=1.57, (95% CI 1.11-2.2) (p=<0.001). The cumulative incidence of acute renal failure was 43.4% in exposed patients and 18.3% in non-exposed patients, with a RR=2.37 with a (95% CI 1.65-3.4) (p<0.001).

Conclusion: There is an association between the development of hyperchloremia and the outcomes of mortality and acute renal failure in critically ill patients.

Keywords: Hyperchloremia, mortality, critical patient, kidney failure, SARS CoV 2.

Ronald Antonio Medina-Lombo,[1] Edward Julián Blanco-Pinzón,[2] Angie Tatiana Ortiz-Palacios,[2] Diana Catalina Sanabria-Waldron,[3] Ana María Morales-Saenz,[4] Alejandra María Soto Morales[5]

[1]Assistant Instructor, Department of Critical Medicine and Intensive Care, University Foundation of Health Sciences, Colombia
[2]Fourth Year Resident of Critical Medicine and Intensive Care, Foundation of Health Sciences, Children's Hospital Universitario de San José, Colombia
[3]Second Year Fellow of Critical Medicine and Intensive Care, Foundation of Health Sciences, Children's Hospital Universitario de San José, Colombia
[4]Hospital physician Hospital de San José, Colombia
[5]Associate professor, University of Tolima, Faculty of Health Sciences, Colombia

Correspondence: Ronald Antonio Medina-Lombo, Assistant Instructor, Department of Critical Medicine and Intensive Care, University Foundation of Health Sciences Children's Hospital Universitario de San José, Bogotá D.C, Colombia, Email medinaronald201@gmail.com

Received: November 02, 2022 | **Published:** November 15, 2022

Introduction

Patients treated in the ICU receive multiple managements for their underlying disease, however, these interventions can develop undesirable effects.[1] Among the most common are crystalloids associated in some patients with unfavorable events such as the development of acute renal failure,[2,3] hydroelectrolytic alterations,[4] acid-base balance,[5] immunological[6-9] and coagulation[10,11] edema[2,3] local microrheology disorders and death. Regarding the latter, there are several studies that describe this relationship, Huang, K et al. found an association between hyperchloremia and 30-day mortality in patients with ischemic stroke,[12] Ditch et al. found a similar association, regardless of the development of dysnatremia.[13] Kim HJ's study describes an increase in mortality in a 30-day follow-up period close to 8% for each 1-mmol/L increase in chlorine in the first 72 hours of admission.[14] Haller et al. describe an association between hyperchloremia and acute renal failure and number of hospital days, calculating a relative risk (RR) of 1.91 (95% CI: 1.01-3.59) for acute renal failure and hospital days (16 days vs 12 days, p=0.03); however, they failed to establish the association between hyperchloremia and mortality.[15]

In Colombia, there is a single retrospective cohort study led by Medina et al., in which the relationship between hyperchloremia and mortality in critical patients was analyzed, finding a RR=3.12 (CI=95% 2.16-4.49) (p<0.001) for mortality and a RR =1.76 (CI=95% 1.42-2.17) (p<0.001) regarding the development of acute renal failure.[16]

Methods

Analytical prospective cohort study developed in the ICUs of the San José University Children's Hospital and the San José Hospital Surgery Society in the city of Bogotá, Colombia, in the period between June 1, 2019 and August 31, 2021. The study population was adult patients who at the time of admission had serum chloride less than 107 meq/L, without renal dysfunction. Patients from other ICUs, undergoing renal replacement therapy or plasma exchange were excluded. The sample size was calculated with the Tamamu program, yielding a sample size of 291 patients; Considering possible losses to follow-up, data from 20% more patients were recorded.

The data collection instrument was built with the variables of interest, and the patients were followed up from admission to the ICU until discharge. The exposure variable was hyperchloremia, defined for this study as serum chloride value ≥107 meq/L; The outcome variables were discharge status defined as alive or dead and the presence of acute renal failure, understood as an increase in serum creatinine levels compared to admission of 1.5 to 1.9 times or ≥0.3 mg/dl or urinary flow rate <0.5 ml/kg/h for 6 to 12 hours (AKIN).

The clinical variables studied were average days of ICU stay, presence of surgical pathology, sepsis, dysnatremia (defined as serum sodium <132 and >145 meq/liter) and APACHE II score in the first 24 hours of ICU stay. The information was registered in a database in Microsoft EXCEL®. The analysis of the information was carried out with the statistical package JAMOVI. Absolute and relative frequencies were used to describe the qualitative variables; for quantitative measures of central tendency and dispersion. The cumulative incidence of hyperchloremia for the entire cohort, the cumulative incidence of acute renal failure, and the incidence of mortality among exposed and unexposed were calculated. The relative risk RR was obtained as the mean of association, accepting statistical significance with a value p < 0.05.

In accordance with resolution 8430 of 1993, which establishes the scientific, technical, and administrative standards for health research, this study was classified as risk-free research. The study was approved by the Ethics and Research Committee of Hospital San José, University Foundation of Health Sciences (FUCS).

Results

Data were collected from 325 patients, 145 belonging to the exposed group and 180 to the non- exposed group. The clinical characteristics of the population are shown in Table 1.

Table 1 Frequency distribution of the clinical characteristics of the study population. 2019-2021

Variable	without hyperchloremia (n=180)	with hyperchloremia (n=145)	Total (n=325)
Age mean (DE)	56,4±17,4	58,6±17,2	57±17
Gender male (%)	106 (58,5)	79 (54,4)	185 (56,9)
Mean days of ICU stay (DE)	8,6±9,2	15,1±14,7	11,4 ±1 2,3
APACHE II mean (DE)	9,9±5,2	11,7±5,8	10,7±5,6
Sepsis (%)	41 (22,7)	45 (31)	86 (26,4)
Surgical patient (%)	60 (33,3)	56 (38,6)	116 (35,6)
Dysnatremia (%)	62 (34,4)	79 (54,4)	141 (43,3)

Data were collected from 325 patients, 145 belonging to the exposed group and 180 to the non- exposed group. The clinical characteristics of the population are shown in Table 1.

SD, Standard deviation

The cumulative incidence of hyperchloremia and renal failure in the entire study population was 44.6% and 29.5%, respectively. The cumulative incidence of death in the exposed group was 36.5% and 23.3% in the unexposed group, with a RR=1.57, (CI=95% 1.11-2.2) (p <0.001). The cumulative incidence of kidney failure was 43.4% in the exposed group and 18.3% in the unexposed group, with a RR of 2.37 with a (95% CI 1.65-3.4) (p<0.001) (Table 2).

Table 2 Mortality and acute renal failure in relation to hyperchloremia. Patients with SARS-Cov 2 infection. Bogotá 2019-2020.

	without hyperchloremia (n=180)	With Hyperchloremia (n=145)	RR	IC 95%	valor p
Mortality (%)	42 (23,3)	53 (36,5)	1,57	1,11-2,2	<0,001
Acute kidney failure (%)	33 (18,3)	63 (43,4)	2,37	1,65-3,4	<0,001

RR, Relative Risk

Discussion

The present study established the association between hyperchloremia and the outcomes of mortality and acute renal failure. The incidence of hyperchloremia was similar to that described by Aguilar,[17] De Vasconcelos and Skinner.[18] However, it is superior to the results of the works described by Neyra and Tani.[19,20] Regarding the association between hyperchloremia and mortality, the study presents a similar RR to the investigations of Aguilar (RR=1.88; CI=1.41-2.51)[17] and Medina in a cohort with characteristics similar to the the of the current work, in which they found (RR=3.12; CI=95%: 2.16-4.49).[16] Regarding the association with kidney failure, the results of this study agree with those of Haller, with a RR=1.91 (CI=95%: 1.01-3.59)[15] and Medina with a RR= 1.76 with a CI=95%: 1.42-2.17.[16]

Based on these results, it can be stated that chloride disturbances are associated with a higher risk of negative outcomes in critical medicine. Therefore, it is important to select the crystalloid to be infused, considering solutions with electrolyte concentrations closer to physiological ones, Ringer's lactate (104 meq/L), compared to normal saline (154 meq/L), which which could reduce the probability of the development of hyperchloremia. With the results analyzed, serum chloride could be considered as an important marker of mortality to be included in the main validated prognostic scales used by ICUs: APACHE (Acute Physiology and Chronic Health Evaluation), SAPS (Simplified Acute Physiology Score), MPM (Mortality Probability Models) and SOFA (Sequential Organ Failure Assessment) or be included in the development of new scales in the future. Additionally, its measurement should be part of the routine follow-up of critically ill patients in ICUs, from admission to discharge. The current pandemic that the world is suffering and the great fields of research to which it has given rise, leaves the door open to expand the sample size of this subgroup of patients and study the possible association between the development of hyperchloremia, and an increase in harsh outcomes in relation to this condition.

Limitations

The present study does not control for confounding between exposure variables and outcomes; including a greater number of patients in the study involving other institutions can optimize the calculation of epidemiological measures, showing statistically significant relationships.

Conclusion

The results of the study, compared with current evidence, reinforce the hypothesis regarding the development of hyperchloremia in critically ill patients and the association with mortality and acute kidney failure. It also suggests that monitoring of chlorine levels can be recorded early and changes can be made in the crystalloid to be infused, reducing the risk of developing hyperchloremia with the side effects that it entails.

Thanks

Conflict of interest statement

All researchers declare no conflicts of interest.

Project financing statement

This project received no institutional funding.

References

1. Dennis RJ PA, Rowan K, Londoño D, et al. Factores asociados con la mortalidad hospitalaria en pacientes admitidos en cuidados intensivos en Colombia. *Archivos de Bronconeumología.* 2002.

2. Trujillo–Zea JA A–HN, Fonseca–Ruiz N. Lactato de Ringer versus solución salina normal para trasplante renal. Revisión sistemática y metaanálisis. *Revista Colombiana de Anestesiología.* 2015;39(5):303–315.

3. Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med.* 2013;369(13):1243–1251.

4. Kellum JA. Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved short–term survival and acid–base balance with Hextend compared with saline. *Crit Care Med.* 2002;30(2):300–305.

5. Finfer S, Liu B, Taylor C. Resuscitation fluid use in critically ill adults: an international cross–sectional study in 391 intensive care units. *Crit Care.* 14; 2010.

6. Kellum JA, Song M, Almasri E. Hyperchloremic acidosis increases circulating inflammatory molecules in experimental sepsis. *Chest.* 2006;130(4):962–967.

7. Kellum JA, Song M, Li J. Lactic and hydrochloric acids induce different patterns of inflammatory response in LPS–stimulated RAW 264.7 cells. *Am J Physiol Regul Integr Comp Physiol.* 2004;286(4):686–692.

8. Aiken ML, Painter RG, Zhou Y, et al. Chloride transport in functionally active phagosomes isolated from Human neutrophils. *Free Radic Biol Med.* 2012;53(12):2308–2317.

9. Pedoto A, Caruso JE, Nandi J, et al. Acidosis stimulates nitric oxide production and lung damage in rats. *Am J Respir Crit Care Med.* 1999;159(2):397–402.

10. Waters JH, Gottlieb A, Schoenwald P, et al. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. *Anesth Analg.* 2001;93(4):817–822.

11. Martin G, Bennett–Guerrero E, Wakeling H, et al. A prospective, randomized comparison of thromboelastographic coagulation profile in patients receiving lactated Ringer's solution, 6% hetastarch in a balanced–saline vehicle, or 6% hetastarch in saline during major surgery. *J Cardiothorac Vasc Anesth.* 2002;16(4):441–446.

12. Huang K, Hu Y, Wu Y, et al. Hyperchloremia Is Associated with Poorer Outcome in Critically Ill Stroke Patients. *Front Neurol.* 2018;9:485.

13. Ditch KL, Flahive JM, West AM, et al. Hyperchloremia, not Concomitant Hypernatremia, Independently Predicts Early Mortality in Critically Ill Moderate– Severe Traumatic Brain Injury Patients. *Neurocrit Care.* 2020;33(2):533–541.

14. Kim HJ, Oh TK, Song IA, et al. Association between fluctuations in serum chloride levels and 30–day mortality among critically ill patients: a retrospective analysis. *BMC Anesthesiol.* 2019;19(1):79.

15. Haller JT, Smetana K, Erdman MJ, et al. An Association Between Hyperchloremia and Acute Kidney Injury in Patients With Acute Ischemic Stroke. *Neurohospitalist.* 2020;10(4):250–256.

16. Ronald Antonio, Luisa Fernanda. Hipercloremia y mortalidad en la unidad de cuidados intensivos. *Revista Colombiana de Anestesiología.* 2018.

17. Aguilar A, Góngora Mukul JJ, López Avendaño VG, et al. Asociación de los niveles elevados de cloro plasmático, en la gravedad y mortalidad de pacientes adultos en la Unidad de Cuidados Intensivos. *Revista de la Asociación Mexicana de Medicina Crítica y Terapia Intensiva.* 2015.

18. Vasconcellos K, Skinner DL. Hyperchloraemia is associated with acute kidney injury and mortality in the critically ill: A retrospective observational study in a multidisciplinary intensive care unit. *J Crit Care.* 2018;45:45–51.

19. Kim HJ, Oh TK, Song IA, et al. Association between fluctuations in serum chloride levels and 30–day mortality among critically ill patients: a retrospective analysis. *BMC Anesthesiol.* 2019;19(1):79.

20. Tani M, Morimatsu H, Takatsu F, et al. The incidence and prognostic value of hypochloremia in critically ill patients. *Scientific World Journal.* 2012;2012:474185.