Published in final edited form as:

Crit Care Med. 2016 January ; 44(1): e53–e54. doi:10.1097/CCM.0000000000001447.

Response to Hyperchloremia versus Non-hyperchloremia or Hyperchloremia versus Normochloremia?

Javier A. Neyra, MD¹, Fabrizio Canepa-Escaro, MD², Jerry Yee, MD³, and Lenar Yessayan, MD, MS^{3,4} for the Acute Kidney Injury in Critical Illness Study Group

¹Division of Nephrology, University of Texas Southwestern Medical Center, Dallas, Texas, USA

²Department of Internal Medicine, Asante Health System, Grants Pass, Oregon, USA

³Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, Michigan, USA

⁴Division of Pulmonary and Critical Care Medicine, Henry Ford Hospital, Detroit, Michigan, USA

We reviewed Jo and colleagues (1) correspondence in which they raised an important question regarding the contribution of hypochloremia to our analysis (2). In our original study (n =1,940), we stratified our primary cohort by the presence (n =615) or absence (n =1,325) of hyperchloremia (serum chloride ≥ 110 mEq/L) on intensive care unit (ICU) admission. Jo and coworkers suggested that the strength of the association between higher serum chloride levels and hospital mortality in the hyperchloremic group may perhaps be stronger if patients with hypochloremia were excluded from the non-hyperchloremic group for comparison.

Consequently, we identified 361 patients with hypochloremia (serum chloride < 100 mEq/L) on ICU admission in our primary cohort. To eliminate the effect of hypochloremia in our results, we performed a sensitivity analysis in a secondary cohort that excluded patients with hypochloremia on ICU admission. This secondary cohort consisted of 615 patients with hyperchloremia and 964 with normochloremia (101 – 109 mEq/L) on ICU admission. We obtained similar results and nearly identical univariate and multivariate logistic regression estimates for the association of higher serum chloride levels with hospital mortality in the hyperchloremic group as our published results (Table 1).

Small observational studies have demonstrated the association between hypochloremia and mortality in critically ill and postoperative patients (3, 4). Jo and colleagues raised the question of a possible bimodal effect of serum chloride levels on mortality outcomes. However, in our primary cohort, there was no association between serum chloride levels at 72 h and hospital mortality in the hypochloremic group (n =361): the univariate odds ratio for each 5 mEq/L decrease in serum chloride was 0.96 (95% CI 0.77 – 1.21).

Address correspondence to: Javier A. Neyra, MD, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX, USA 75390, Tel: 214-645-5418, Fax: 214-645-8903, javier.neyralozano@utsouthwestern.edu Or to Lenar Yessayan, MD, MS, Henry Ford Hospital, 2799 W Grand Blvd., Detroit, Michigan, USA 48202, Tel: 313-916-7134, Fax: 313-916-2554, lyessay1@hfhs.org.

Conflicts of Interest: The authors declare that they have no relevant financial interests.

Copyright form disclosures: The authors have disclosed that they do not have any potential conflicts of interest.

In regards to the study by Tani and coworkers (4), it comprised interesting observations of serum chloride levels and adverse hospital outcomes in critically ill patients. Importantly, in the multivariate model, serum chloride was not independently associated with hospital mortality. However, the authors also reported the incidence of hospital mortality in three subgroups (hypochloremia, normochloremia, and hyperchloremia) and found the highest risk for mortality in the hypochloremic group. The risk for hospital mortality was not different between the normochloremic and hyperchloremic groups: 14/364 (3.8%) versus 3/81 (3.7%). The lack of difference between these two subgroups is statistically evident by Fisher's exact test ($p = 1.00$). We consider that this work constitutes a negative study for the association between hyperchloremia and hospital mortality as discussed in our manuscript (2).

Acknowledgments

Source of Funding: Research reported in this publication was supported by the University of Texas Southwestern Medical Center O'Brien Kidney Research Core Center (NIH, P30 DK079328-06), the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH, UL1TR001105), and the Division of Nephrology and Hypertension of Henry Ford Hospital. The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health, the University of Texas Southwestern, or Henry Ford Hospital. JAN is supported by the Ben J. Lipps Research Fellowship Program of American Society of Nephrology Foundation for Kidney Research and the Truelson Fellowship Fund at the Charles and Jane Pak Center of Mineral Metabolism and Clinical Research.

References

1. Jo S, Jeong T, Lee JB, et al. Hyperchloremia versus Non-hyperchloremia or Hyperchloremia versus Normochloremia? Crit Care Med. 2015 in press.
2. Neyra JA, Canepa-Escaro F, Li X, et al. Association of Hyperchloremia With Hospital Mortality in Critically Ill Septic Patients. Crit Care Med. 2015; 43(9):1938–1944. [PubMed: 26154934]
3. Kimura S, Matsumoto S, Muto N, et al. Association of serum chloride concentration with outcomes in postoperative critically ill patients: a retrospective observational study. J Intensive Care. 2014; 2(1):39. [PubMed: 25908989]
4. Tani M, Morimatsu H, Takatsu F, et al. The incidence and prognostic value of hypochloremia in critically ill patients. The Scientific World Journal. 2012; 2012:474185. [PubMed: 22701359]

Table 1

Association of hospital mortality with serum chloride levels at 72 h of intensive care unit stay in a secondary cohort (n=1,579) in which patients with hyponatremia (serum chloride < 100 mEq/L) on admission were excluded

	<i>Normochloremia on admission (Cl₀ 101 – 109 mEq/L) Odds Ratio</i>	<i>P-value</i>	<i>Hyperchloremia on admission (Cl₀ 110 mEq/L) Odds Ratio</i>	<i>P-value</i>
Cl₇₂ per 5 mEq/L increase <i>Univariate</i>	1.05 0.93 – 1.30	0.26	1.38 1.13 – 1.68	0.002*
Cl₇₂ per 5 mEq/L increase <i>Multivariate</i>	1.06 0.87 – 1.30	0.05	1.27 1.02 – 1.59	0.03*

Cl₀ =serum chloride on ICU admission; Cl₇₂ =serum chloride at 72 hours of ICU stay

* Statistically significant, P-value < 0.05

Multivariate models adjusted for age, gender, hypertension, acute kidney injury (Kidney Disease Improving Global Outcomes serum creatinine-based criteria), oliguria, cumulative fluid balance, vasopressor or inotrope requirements, mechanical ventilation, SOFA score, and base deficit. Multivariate models included all variables associated with hospital mortality on univariate analysis at P-value < 0.10