Has the time come to abandon chloride-rich resuscitation fluids?

Michael Heung, Lenar Yessayan

Department of Medicine, Division of Nephrology, University of Michigan, Ann Arbor, MI, USA

Correspondence to: Michael Heung, MD, MS. 1500 E. Medical Center Drive, SPC 5364, Ann Arbor, MI 48109-5364, USA. Email: mheung@umich.edu.

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Over the past several years, there has been an increasing focus on the potential impact of resuscitation fluid composition on outcomes in critically ill patients (1-3). Chloride is the most abundant anion in the extracellular fluid, and plays an essential role in many body functions including acid-base balance, muscular activity, osmosis, and immunomodulation (4). Yet in both animal models and observational clinical studies, the use of hyperchloremic (physiologically "unbalanced") solutions has been linked to increased risk of acute kidney injury (AKI) and/or mortality. However, these associations have not been consistent across studies, and have not been confirmed in clinical trial settings (5). Currently, in the United States, 0.9% saline (chloride content 154 mEq/L) remains the predominant solution used for resuscitation in critically ill patients.

In a recent issue of *Critical Care Medicine*, Sen and colleagues contribute further to this area by examining the association between total chloride load and outcomes (6). Using a robust single-center clinical database, the authors identified 4,710 critically ill non-surgical patients who received at least 60 mL/kg fluid resuscitation within a 24 hour period. They calculated each patient's absolute chloride load based on the chloride concentration and volume of each administered fluid. In unadjusted analyses, greater chloride load was associated with increased risk for hyperchloremic metabolic acidosis, AKI and all-cause mortality. After adjusting for age, volume of administered fluid and baseline severity of illness, there was no longer a significant association between chloride load and hyperchloremic metabolic acidosis or AKI. However, chloride load remained a predictor of mortality (adjusted HR, 1.055 per 100 mEq of administered chloride, P=0.0015), and this relationship persisted out to one year. How do these findings compare to the existing literature? Is there now enough evidence to steer clinicians away from the use of chloride-rich resuscitation fluids?

A number of large observational studies have associated chloride-rich crystalloid solutions, chloride load and hyperchloremia with increased hospital mortality and/or with AKI. Perhaps most comparable to the Sen study, Raghunathan and colleagues examined non-surgical critically ill patients with sepsis and, using propensity-matching (n=6,730), reported the same association between the use of chloride rich solutions and increased risk for hospital mortality but not AKI (2). Importantly, both the Sen and Raghunathan studies observed a dose-response relationship, whereby increasing chloride association was associated with progressive increased mortality risk. In another study, Neyra and colleagues showed an association between worsening hyperchloremia and hospital mortality in critically ill patients with severe sepsis admitted with hyperchloremia, independent of cumulative fluid balance (7). Shaw and colleagues also demonstrated an association between higher intravenous chloride load and hospital mortality (8). However, that study focused on peri-operative fluid administration in patients undergoing abdominal surgery. In addition to greater mortality, use of a chloride-rich solution (0.9% saline) was associated with greater peri-operative complications including metabolic acidosis, infection and AKI requiring dialysis (8).

In contrast to the above studies, other observational

studies have not shown an association between chloride administration and mortality. In a prospective single-center study of quasi-experimental design, Yunos and colleagues reported a lower incidence of AKI (8.4% *vs.* 14.0%, P<0.001) when a chloride-restrictive fluid strategy was implemented in the intensive care unit; however, no differences in mortality were seen (1). A recent meta-analysis of 21 studies (6,253 patients) found that administration of chloride-rich fluids was associated with increased risk for hyperchloremic acidosis and AKI but not mortality (3). Most recently, in a retrospective cohort study, Shao *et al*. reported a positive association between serum chloride level and AKI (9). Interesting, in this study severe hypochloremia was also associated with increased AKI risk. As such, there may be a population that can benefit from resuscitation with chloride-rich fluids. Notably, most published studies, including the Sen study, do not account for baseline chloride levels in the analysis.

An inherent limitation to observational studies is the inability to rule out residual confounding as an explanation for the results. Given the inconsistent findings between observational studies, there appears to be ample equipoise to conduct clinical trials. The 0.9% Saline versus Plasma-lyte 148 for Intensive Care Unit Fluid Therapy (SPLIT) trial was a clustered randomized controlled crossover study comparing saline with buffered crystalloid solutions for routine administration in critically ill patients. In that study, both groups had similar rates of AKI and there was also no statistically significant difference in hospital mortality (5). However, this study included a heterogeneous population that required relatively little fluid administration (average 2L) and only 4% had sepsis. The low quantity of fluids administered and the low severity of illness in the study population seriously affect the generalizability of the results. In contrast, the Sen study specifically focused on a higher acuity population receiving substantially more fluid resuscitation. As such, differences in the patient population may explain the different conclusions from these studies, and despite the randomized design, the SPLIT trial does not inform the choice of solutions to use in critically ill patients requiring large volume resuscitation.

Beyond statistical associations, what is the biologic plausibility linking chloride administration to harmful outcomes? Proposed mechanisms include renal vasoconstriction leading to renal hypoperfusion and renal interstitial edema leading to intracapsular hypertension (10-13). While this would explain the association between chloride load and AKI, the pathophysiologic mechanisms linking chloride load and mortality (independently of AKI) are less clear. Augmented pro-inflammatory response (14), and diminished coagulation ability (15) have been observed in hyperchloremic metabolic acidosis but the clinical significance of these findings remains uncertain. Thus, there is not a clear causal link to explain the findings in the Sen study of an association between chloride load and mortality.

At present, there remains a lack of clear randomized clinical trial evidence to guide choice of resuscitation fluid administration. The Sen study has further contributed to a growing body of observational literature linking chloride load with adverse outcomes, particularly in critically ill patients. Despite the inconsistencies in reported outcomes, it is notable that nearly all studies suggest an association with adverse outcomes and there are no studies that report beneficial effects of chloride-rich fluids compared to balanced solutions—in other words, no evidence of benefit, but quite possibly some harm. Until more definitive evidence is available from clinical trials, clinicians may wish to minimize chloride load when administering large amounts of crystalloids or in patients who present with hyperchloremia.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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