A Salty Start to Resuscitation: Does It Matter?

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The utility of balanced crystalloids and 0.9% sodium chloride (NS) in the management of septic shock has been extensively studied, including the comparative outcome of mortality. The Isotonic Solutions and Major Adverse Renal Events Trial (SMART) study was a cluster-randomized, multiple crossover trial comparing balanced solutions to NS in various ICUs. This large prospective study found that balanced solution was associated with a reduction in major adverse kidney events within 30 days (death included in this composite outcome) (1). A subanalysis of septic patients in the SMART study showed that balanced crystalloid use in the emergency department and throughout the ICU admission was associated with a lower 30-day in-hospital mortality compared with NS (26.3% vs. 31.2%; adjusted odds ratio, 0.74; 95% CI, 0.59–0.93; $p = 0.01$) (2). Of note, the primary balanced crystalloid used in the SMART trial was lactated Ringer's (LR). Consequently in 2021, the Surviving Sepsis Campaign guidelines also recommend the use of balanced crystalloids over NS for fluid resuscitation in sepsis, citing the potential benefits in reducing mortality and renal complications (3).

Unfortunately, not all studies comparing balanced solutions with NS have shown a clear benefit on mortality. A 2022 comprehensive meta-analysis showed that balanced crystalloids were associated with reduced overall mortality (risk ratio, 0.88; 95% CI, 0.81–0.96) when compared with NS in septic patients. However, when only evaluating the eight randomized controlled trials within this meta-analysis, no statistically significant difference in outcomes was found (4). Similarly, the recent Balanced Solution in Intensive Care Study (BaSICS) showed no difference in 90-day mortality when comparing balanced solutions with NS in an overall critically ill population (5). From these data, we see that the best approach to fluid management may be complicated, include several variables, and be population-dependent.

One variable of particular interest is the initial fluid resuscitation type received in the prehospital and early hospital setting. To investigate the effects of balanced vs. NS solutions in this time frame, a secondary analysis of the septic population in the SMART study was conducted. This analysis revealed that the beneficial effects of balanced crystalloids on mortality were more pronounced when fluid choice was controlled starting in the emergency department and continued in the ICU, compared with when fluid choice was controlled only in the ICU. These findings point toward additional benefit of balanced fluids in early resuscitation (6). Similarly, a secondary analysis of the BaSICS trial found a high probability of a 90-day mortality benefit for patients in the balanced solution arm who exclusively received balanced solution prior to trial enrollment (7). Finally, a retrospective analysis of 60,000 patients with septic shock between 2006 and 2010 found lower in-hospital mortality when balanced

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crystalloids were a part of initial fluid resuscitation (8). These analyses have provided a consistent indication that the choice of initial fluid type may be an important clinical decision.

In this issue of *Critical Care Medicine*, Gelbenegger et al (9) adds to the body of evidence suggesting that early fluid resuscitation choice matters. This secondary analysis of the Crystalloid Liberal or Vasopressor Early Resuscitation in Sepsis (CLOVERS) trial aimed to determine if the initial fluid resuscitation choice with either LR or NS solution was associated with a difference in outcomes in patients with hypotension due to sepsis (9). In the CLOVERS trial, patients were randomized to a fluid restrictive or liberal management strategy within 4 hours of identification of sepsis-induced hypotension refractory to initial fluid resuscitation. Patients were required to have received at least 1 L and no more than 3 L of IV fluid within 24 hours of hospitalization for inclusion (10). This analysis compared the outcomes associated with LR or NS as the initial 1–3 L of resuscitation before randomization. The primary outcome was 90-day all-cause mortality. The secondary outcomes included days free from the ventilator, vasopressors, the ICU, and the hospital at 28 days. The authors also investigated the incidence of acute kidney injury and compared several laboratory chemistries between groups (9).

Of the patients included in the CLOVERS trial, 622 received LR and 690 received NS solution. Although baseline characteristics were generally similar, chronic kidney disease (CKD) was more common in the saline group. The 90-day all-cause mortality rate was 12.2% in the LR group compared with 15.9% in the NS group (adjusted hazard ratio [HR], 0.71; 95% CI, 0.51–0.99, $p = 0.043$). The Kaplan-Meier curve for this outcome appears to separate well within the first 2 weeks after initial fluid administration. However, the adjusted HR was no longer statistically significant after adding CKD as an independent covariate to the model (HR, 0.73; 95% CI, 0.52–1.01). The sensitivity analysis also became non-significant with omission of several individual factors (sex, Charlston comorbidity index, Glascow Coma Scale, blood pressure, and the amount of fluid after randomization). LR was associated with more hospital-free days at day 28 compared with NS with an adjusted mean difference of 1.6 days (95% CI, 0.4–2.8; $p = 0.009$). Other secondary endpoints were not statistically significantly different, but the NS group did have higher serum chloride and decreased serum bicarbonate levels compared with the LR group. Because this was a secondary analysis and due to the sensitivity analysis, the authors acknowledged that these results are primarily hypothesis-generating (9).

This study provides a continued signal of the potential benefit of using balanced fluids from the very start of sepsis resuscitation, as we have seen similar findings in the above-mentioned secondary analyses of the SMART and BaSICS trials (6, 7). However, this analysis differs from the other secondary analyses because the purpose of the primary CLOVERS trial was not intended to compare crystalloid fluid types. The CLOVERS study compared restrictive and liberal fluid resuscitation strategies in sepsis-induced hypotension and found no difference in 90-day mortality between the groups (10). Because the primary treatment provided similar outcomes, patients were grouped only according to their initial fluid type in this study (although the assigned treatment group was included in the COX regression model for 90-d mortality) (9). This difference is potentially significant as it may provide insight into the importance of the initial fluid resuscitation choice regardless of subsequent fluid selection or strategies through the trial enrollment period. It suggests that targeting balanced solutions from the prehospital or early hospital setting may have an early mortality benefit that persists long-term, regardless of fluid choices later in care. Combined with the previous literature, this would again support the overall concept that fluid choice matters at all points and supports the current recommendations of the Surviving Sepsis Campaign (3).

When taking a step back to examine all critically ill patients, one might consider that if crystalloid fluid resuscitation choice is THAT important, why have all large prospective studies comparing balanced and saline solutions not clearly found a difference in outcomes? Why would even EARLY fluid choice specifically make a lasting difference? While we do not have a clear answer to these questions, it is becoming increasingly clear that fluid choice in resuscitation is complicated clinically and, thus, makes clinical trials on this topic complex. From various human and animal studies it appears that chloride concentrations may affect renal perfusion, acid–base balance, and hepatic cytokine production (11, 12). It may be that these factors are especially important during the very early course of sepsis and other disease states when organ perfusion is initially compromised. Hence, care is warranted when interpolating the results of these large,

nonspecific, diverse trials onto the septic shock population. It also may be that other components and properties of fluids (volume, osmolality, electrolyte components, protein, and administration method) may play a role in a particular benefit or harm to an individual patient situation at an individual point and time. For example, a subgroup of analysis of the CLOVERS trial for patients with advanced CKD (estimated glomerular filtration rate of less than 30 mL/min/1.73 m^2 or history of end-stage renal disease on chronic dialysis) revealed lower mortality for those patients in the restrictive volume arm (HR, 0.5; 95% CI, 0.29–0.85) (13). Indeed, this variable may have impacted outcomes in the current subanalysis, as well. Those that have attempted to retrospectively investigate components of early fluid resuscitation have also demonstrated how difficult and complex this concept can become with multiple different variables occurring simultaneously (8, 14). The question of balanced vs. saline solutions may be only a piece of the resuscitation puzzle in an individual patient. As a result, we see repeated signals of overall benefits in patients rather than a consistently bright-burning light directing the resuscitation pathway.

Although large randomized prospective studies targeting this initial resuscitation period would be ideal, it can be difficult to target the desired septic shock population due to the need to initially predict fluid responsiveness and requirements throughout the disease process. As mentioned, it is also difficult to investigate a single fluid choice in isolation of other fluid variables. At this point, the investigations comparing balanced and 0.9% NS solutions in early fluid resuscitation are consistent enough to indicate that the composition of these first few liters makes a clinical difference in many patients. As a result, balanced crystalloid solutions should continue to be considered early in patients with sepsis-induced hypotension.

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