

Saline Is the Solution for Crystalloid Resuscitation

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Fluid resuscitation is a fundamental component of the management of acutely ill patients. The choice of fluid has been an issue of longstanding debate (1). With respect to the choice of crystalloid for fluid resuscitation, such debate has often been framed around the notion that saline is “*less physiologic*” than the other commercially available crystalloids (2). However, although 0.9% saline has approximately 1.5 times the chloride concentration of human plasma, the lactate concentration of Ringer lactate is 28 times that of plasma, and the acetate concentration in Plasma-Lyte 148 (Baxter, Deerfield, IL) and Normsol-R (Hospira Inc, Lake Forest, IL) exceeds that found in plasma by as much as 1,000 times (3). In other words, none of the commercially available crystalloids are inherently more physiologic than the others.

There is little doubt that 0.9% saline administration has effects on acid-base physiology (4). Because 0.9% saline has a strong ion difference of zero, its administration would be expected to cause metabolic acidosis (4), and indeed, the development of mild or even moderate hyperchloremic metabolic acidosis is often observed at the bedside in critically ill patients who have received moderate volumes of IV saline. That said, in the Saline versus Albumin Fluid Evaluation study (5), even when 0.9% saline was used for fluid resuscitation in ICU, there was a significant increase in serum bicarbonate and base excess over time after randomization, often leading to significant metabolic alkalosis (6). As balanced crystalloids have a positive strong ion difference compared with saline (7), it seems likely that large volumes of balanced crystalloids will exacerbate this common acid-base disturbance among critically ill patients compared with saline.

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As well as its effects on acid-base physiology, 0.9% saline may affect renal physiology because chloride seems to have an important role in tubuloglomerular feedback mechanisms (8). Specifically, the chloride concentration in the fluid delivered to the distal tubule seems to be one mediator of tubuloglomerular feedback. As the chloride concentration in the distal tubule fluid rises, feedback occurs via the macula densa, the afferent arteriole constricts, and the glomerular filtration rate drops (9, 10). In healthy volunteers, renal artery blood flow velocity and renal cortical tissue perfusion fall after administration of 2 L of 0.9% saline but not after administration of 2 L of a buffered crystalloid (11).

These effects on biochemistry and acid-base physiology are not in dispute, but there is little evidence that they translate into clinically important effects on patient-centered outcomes (8). When it comes to large-scale randomized controlled trials, 0.9% saline has been administered to more than 8,000 ICU patients without any evidence, suggesting that it results in worse outcomes for patients than its comparator (5, 12, 13). Indeed, 0.9% saline was associated with a reduced risk of death and disability compared with albumin in patients with traumatic brain injury (14) and with a reduced risk of requiring renal dialysis compared with hydroxyethyl starch (Voluven) in an all-comers population of critically ill adults requiring fluid resuscitation (12).

In the Saline versus Plasma-Lyte 148 for Intensive care unit fluid Therapy (SPLIT) trial, there were no differences in patient-centered outcomes between the treatment groups in 2,278 critically ill patients (13). There was, however, one patient in the Plasma-Lyte 148 group who died after a serious adverse event judged by the treating clinician to be potentially related to study treatment. This patient developed severe lactic acidosis and progressive multiple organ failure culminated in circulatory collapse and death with no specific cause of death identified at autopsy. Hyperlactemia occurring in association with sodium acetate infusion has been reported previously (15).

The overall exposure to the study fluids in the SPLIT trial was small (a median of 2 L), and the study population had low illness acuity. As a result, further large randomized trials are needed to assess the effects of 0.9% saline compared with buffered crystalloids in high-acuity ICU patients receiving larger fluid volumes. Until such trials are conducted, the comparative effectiveness of 0.9% saline and buffered crystalloids in critically ill patients can only be inferred from small-scale randomized controlled trials and observational trials. Apart from

the SPLIT trial, the existing evidence base from randomized controlled trials in critically ill patients comparing saline with other crystalloids is extremely limited with only 293 patients enrolled in such randomized controlled trials in total and no significant difference reported in any clinically important outcome (16).

In the most widely cited observational cohort study removing chloride-rich fluids, including 0.9% saline, from a single ICU was associated with a reduction in the cumulative incidence of acute kidney injury (AKI) and reduced requirements for renal replacement therapy (17). However, in this study, there were differences in albumin use in the pretreatment and post-treatment phases, and one of the fluids whose use was discontinued was a synthetic gelatin-based colloid. The use of gelatins has previously been associated with an increased risk of AKI in patients with sepsis (18), and thus, it is plausible that the observed difference was related to removing gelatin from the ICU not removing 0.9% saline. That said, as multiple changes in fluid therapy occurred simultaneously and the study was an open-label before-and-after trial (17), it is impossible to say with any certainty what component of the fluid change strategy was responsible for the observed changes or even if the fluid therapy was responsible for the observed changes at all.

A recent meta-analysis of randomized controlled trials and observational studies comparing chloride-liberal fluids with chloride-restrictive fluids in perioperative and critical care reported that the use of chloride-liberal fluids was associated with a significant increase in the risk of AKI (16). However, 77% of the patients included in this meta-analysis were from the single centre before and after study described above (17). When this study was excluded, there was no significant effect on AKI (16). Furthermore, two additional studies published since this meta-analysis reported no significant association between choice of IV crystalloid and AKI risk (19, 20). The first study compared 3,365 patients with sepsis treated with balanced fluids with a propensity-matched cohort of 3,365 patients treated with 0.9% saline. The second study evaluated the impact of fluid composition on outcomes in patients with systemic inflammatory response syndrome and included 1,158 0.9% saline-treated patients and 1,158 propensity-matched patients treated with a calcium-free balanced solution as the primary fluid (20).

Although some observational studies have reported an increased mortality risk associated with the use of 0.9% saline (19, 21), the recent meta-analysis reports no overall significant increase or decrease in the risk of in-hospital mortality with the use of high chloride fluid (0.9% saline) compared with low chloride fluid (buffered crystalloid) (risk ratio, 1.13; 95% CI, 0.92–1.39) (16). Overall, there are no consistent signals of harm from 0.9% saline in observational studies, and any potential harms identified need to be considered in light of the inevitable limitations of bias and confounding inherent in all observational studies (22). The patients who received 0.9% saline may be systematically different from the patients who received buffered crystalloids, and the treatments provided by doctors who use 0.9% saline may be different to the treatments provided by doctors who use buffered crystalloids.

Saline (0.9%) is the dominant IV crystalloid fluid in North America (23). Fundamentally, this is a debate about where the threshold for practice change lies. I submit that the current level of evidence falls far below that threshold. The substantial and important work described in the studies outlined in this “Viewpoint” has paved the way for a definitive large-scale randomized controlled trial. The Australian and New Zealand Intensive Care Society Clinical Trials Group will soon begin enrolling patients into the Plasma-Lyte 148 versus saline (PLUS) trial, an 8,800 participant double-blind randomized controlled trial with a primary end point of day 90 mortality. PLUS will definitively establish the relative efficacy and safety of buffered crystalloid compared with 0.9% saline in critically ill patients with high mortality risk. Until the results of PLUS are known, 0.9% saline should remain the first choice for crystalloid fluid resuscitation. It is a choice supported by level I evidence (5, 12). The alternatives are fluids that have either not been shown to be superior to saline in randomized controlled trials in critically ill patients (i.e., Plasma-Lyte 148) (13) or have not been tested in large-scale randomized controlled trials at all (e.g., Ringer lactate). Saline is the first choice crystalloid fluid and is supported by 150 years of clinical experience (24). Our options are to stick with what is tried and tested or to change to more expensive fluids on the basis of inductive physiologic reasoning and observational data that are subject to bias and confounding.

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