Assessing Toxicity of Intravenous Crystalloids in Critically Ill Patients

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Intravenous administration of a specific fluid may have very different effects compared with enteral administration of the same fluid. For example, pure water is well tolerated when given orally, but is highly injurious (leading to hemolysis) when administered intravenously. Intravenous fluids are the most common intervention prescribed for hospitalized patients and may be administered for multiple reasons, such as for rehydration (as an alternative to the enteral route), as a vehicle or carrier for medication delivery, and to produce direct physiologic effects on cardiac output and electrolyte concentrations (as drugs). There are important differences in the composition, volume, and rate of administration of fluids for these different uses.

Over the last 25 years, the safety and efficacy of intravenous fluids have been vigorously debated. First, the composition of lactated Ringer solution was changed from a racemic mixture of lactate ions to pure l-lactate when high concentrations of the d-isomer were found to be toxic, including cardiac and neural toxicity.1 Next, the combination of several small studies examining the use of albumin for fluid resuscitation suggested an association with decreased survival.2 Even though a subsequent large trial showed no overall mortality difference between albumin vs saline for fluid resuscitation of patients in the intensive care unit (ICU), there was evidence of toxicity in 1 predefined subgroup.3 Subsequent analysis including detailed follow-up provided additional evidence that a 4% albumin solution was harmful for patients with increased intracranial pressure, probably related to its hypotonicity and the effect on intracranial pressure.4 More recently, the use of hydroxyethyl starch was found to have an adverse effect on survival among patients with sepsis, apparently related to its effect on acute kidney injury (AKI).5 A subsequent larger trial showed no significant difference between hydroxyethyl starch vs saline administration and mortality, and also demonstrated that hydroxyethyl starch was associated with a reduction in AKI but a small increase in the use of dialysis.6 Importantly, trials showing harm used much larger volumes of starch and studied higher-risk patients.7 As a result, most experts now accept that hydroxyethyl starch is at least mildly nephrotoxic, although disagreement exists as to whether the solution still has a role in the management of some patients.

Isotonic 0.9% sodium chloride (saline) solution is the most commonly used intravenous fluid in much of the world, and especially in North America.8 The toxic potential of sodium chloride solutions was known at least as early as the late 19th century and was described by Cushing9 among others. Although the sodium concentration of isotonic saline is only slightly higher than that of plasma, the higher than physiologic chloride concentration can lead to hyperchloremia and acidosis if isotonic saline is administered fast enough, and in large enough volumes.10 Bolus administration of either isotonic saline or albumin in saline was found to increase short-term mortality in children with sepsis in Africa.11 Although the mechanism of this toxicity is unclear, increased deaths appeared to be mainly related to late cardiovascular collapse—a known consequence of experimental hyperchloremic metabolic acidosis in septic animals.12

Numerous observational studies13-15 and a sequential period trial16 have suggested a signal of potential harm when saline administration was compared with administration of fluids with more physiologic chloride concentrations, although the kinds of adverse outcomes have varied. Some studies have shown increased AKI or dialysis,13,16 whereas other reports have shown increased hospital mortality without an effect on AKI.14 This heterogeneity of effect is important because it demonstrates 2 essential aspects about toxicity—that toxicity is dose dependent and that the manifestation of toxicity depends on the susceptibility of the population exposed. A high “dose” of a low-toxicity substance will cause harm in a susceptible patient, whereas a low dose of a highly toxic substance may be undetectable in a low-risk patient. Put more simply, if there is a hazard with saline administration, then healthier patients who receive small doses will deal with the hazard better than sicker patients who receive large doses.

In this issue of JAMA, Young and colleagues17 report the 0.9% Saline vs Plasma-Lyte 148 for ICU fluid Therapy (SPLIT) trial, a multicenter study comparing 0.9% saline with a buffered electrolyte solution for fluid therapy among 2278 patients who were receiving treatment in 4 ICUs in New Zealand and required crystalloid fluid therapy. The indications for fluid were not specified, but presumably included both volume replacement as well as fluid resuscitation and other indications. The overall exposure to study fluids was small (a median of only 2 L) during the ICU stay, and most of the fluid administration occurred during the first 24 hours. The population was (at most) moderate risk (mean Acute Physiology and Chronic Health Evaluation [APACHE] II score, 14) and predominantly included postoperative patients. Overall, development of AKI within 90 days of enrollment (the primary outcome) occurred in only approximately 9%, and rates
of renal replacement therapy (RRT) and in-hospital mortality (key secondary outcomes) were approximately 3% and 8%, respectively, with no significant differences between the buffered crystalloid group and the saline group (AKI, 9.6% for buffered crystalloid vs 9.2% for saline; RRT, 3.3% for buffered crystalloid vs 3.4% for saline; mortality, 7.6% for buffered crystalloid vs 8.6% for saline).

The study was well conducted with excellent adherence to study protocol and near-complete follow-up, and the results have high face validity. The authors conclude that fluid choice did not alter the risk of AKI and that “further large randomized clinical trials are needed to assess efficacy in higher-risk populations and to measure clinical outcomes such as mortality.” This trial has set the stage for future studies, which should be guided both by the success of the trial in its protocol adherence and pragmatic elegance as well as by its limitations.

However, some important points merit discussion. First, it is unclear how much physiologic separation may have occurred between the 2 fluid administration groups. The authors did not report serum chloride data, which may have allowed an estimate of whether there was sufficient difference between the groups to permit a plausible effect on clinical outcomes. Second, the total exposure to these 2 fluids was minimal, approximately 2 L during the entire ICU stay. It is unlikely that this amount of fluid volume could have demonstrated a plausible hazard, and not in the study population that was at low risk for AKI or other adverse effects. Third, if the trial had been designed to test the efficacy of fluids on renal function, then the authors would have had to measure renal function or injury in a more granular fashion, perhaps including biomarkers or imaging studies. Prior studies in animals or healthy volunteers have shown important effects of fluids on the kidney. If the investigators had used the techniques used by Chowdhury et al, then they would most likely have demonstrated similar changes in renal blood flow and function, but these do not necessarily lead to an increase in moderate-severe AKI, as measured by changes in serum creatinine. In the healthy kidney, substantial functional reserve must be exhausted before serum creatinine increases.

Another concern is whether the trial reported by Young et al is an effectiveness trial. The effectiveness of fluids for treating or preventing AKI would require the presence of (or risk for) fluid responsive AKI, and clinicians would need to understand that they were using the fluid for this indication. Instead, the SPLIT trial enrolled patients who received fluid for a variety of indications and the effectiveness for each indication was not assessed. Rather, adverse events were measured. Thus, the SPLIT trial, like the CHEST and SAFE trials, were actually toxicity studies, or at best were studies that accepted a broad assessment of effectiveness using mortality as a surrogate outcome. The surrogacy of the mortality end point is clear because, if any, patients who are critically ill die for lack of 2 L of crystalloid.

This fundamental premise that large pragmatic studies can be used to assess the effectiveness of fluids on outcomes such as AKI, requirement for dialysis, and mortality should be carefully considered when the intervention is not being used specifically for these purposes. Drugs such as 0.9% saline or other electrolyte solutions might result in differences in these outcomes, but it will be as a result of differences in toxicity, not efficacy, and studies should be designed accordingly. In particular, such studies need to deliver a plausible dose of fluids to a population at sufficient risk for adverse outcomes to uncover the hazard, if one exists. If there is a hazard with one or another of these fluids, then it will be important to discover and quantify that risk, however small, because of the sheer enormity of the exposed population that receive intravenous fluids. This hazard will not be unmasked by treating healthier patients with small doses of fluids, but rather by treating sicker patients with larger fluid volumes.

In the meantime, the results of the trial by Young et al provide reassurance that neither 0.9% saline nor a low-chloride electrolyte solution appears to be particularly hazardous when the total dose used in patients at low to moderate risk is about 2 L. This is an important contribution to the care of patients in the ICU. However, the large body of “circumstantial” evidence that points to a harm signal for saline—with scant, if any, evidence of comparative benefit—should behoove intensivists and other clinicians to proceed with caution when ordering intravenous fluids.

### Article Information

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### References


The Changing Landscape of Noninvasive Ventilation in the Intensive Care Unit

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Traditionally, endotracheal intubation has been used as a treatment for patients with respiratory failure who require mechanical ventilation. Although intubation can be lifesaving, it is also associated with significant morbidity.1 Immuno-compromised patients with acute hypoxemic respiratory failure are at particularly high risk; these patients often require high levels of ventilatory support (ie, positive end-expiratory pressure [PEEP]) and fractions of inspired oxygen (FiO2). Intubated patients usually require sedative medications, analgesic agents, or both and are at risk for many complications seen in the intensive care unit (ICU), such as ventilator-associated pneumonia, ICU-acquired weakness,2 venous thromboembolism,3 delirium, and cognitive dysfunction.4 As such, these patients typically have a high associated mortality, estimated at approximately 50%.5

Therefore, in modern ICU care, noninvasive ventilation is used frequently for the care of patients with acute respiratory failure. Specifically, this intervention can improve gas exchange and reduce the work of breathing without requiring an artificial airway. Consequently, patients treated with noninvasive ventilation may avoid some of the adverse consequences of invasive mechanical ventilation. The most compelling evidence for the benefits of noninvasive ventilation is from studies involving patients with exacerbations of chronic obstructive pulmonary disease6 and acute cardiogenic pulmonary edema.7 The benefits of noninvasive ventilation in hypoxic immunocompromised patients are less compelling. Two small, randomized clinical trials demonstrated that use of noninvasive ventilation was associated with a substantial decrease in rates of endotracheal intubation, ICU complications, and mortality.6,8 However, these studies are old, and other studies that involved a heterogeneous population of patients with acute hypoxic respiratory failure demonstrated high rates of treatment failure with noninvasive ventilation.9,10

Over the last 2 decades, the technology of noninvasive ventilation has changed substantially. The ventilators used in the 1990s delivered pressure through the ventilator circuit with room air as the source of fresh gas flow;4 with flow rates that were relatively low (ie, 10 to 35 L/min). These flow rates could be supplemented by oxygen delivered via a side port tubing connection. However, given that room air was the source of most of the fresh gas flow through the ventilator, the highest FiO2 that could be delivered was typically limited to 30% to 40%. Such ventilators were of limited utility in the care of patients requiring higher FiO2 levels. In addition, the ventilator interface was a rubber face mask that was often prone to air leakage when high pressures were needed.6 In contrast, modern noninvasive ventilation involves use of a ventilator with the fresh gas flow source coming directly from the medical oxygen and medical air sources. These connections allow for high pressure and flow and an FiO2 that can be titrated from 21% to 100% as needed. Furthermore, the interfaces now available for noninvasive ventilation administration include more compliant masks of various sizes; these tend to be much more comfortable, particularly for patients with acute hypoxic respiratory failure, who often require higher levels of PEEP, higher driving pressures, or both.