Fluid as a Drug: Balancing Resuscitation and Fluid Overload in the Intensive Care Setting

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Intravenous fluid resuscitation is ubiquitous throughout medicine and is often considered a benign procedure. Yet, there is now clear recognition of the potential harms of fluid overload after initial resuscitation. In recent years, there has also been an increasing focus on comparing various resuscitation fluids with respect to both benefits and risks. Studies have examined colloids, such as albumin and starches, against the clinical standard of crystalloids. In addition, evidence has emerged to suggest that outcomes may be different between resuscitation with chloride-rich vs balanced crystalloid solutions. In this article, we review the current literature regarding choice of intravenous fluids for resuscitation in the intensive care setting and describe the dangers associated with fluid overload in critically ill patients.

Key Words: Crystalloids, Colloids, Balanced solutions, Resuscitation, Fluid overload

INTRODUCTION

The first intravenous saline solution was likely delivered by Dr. Thomas Latta in 1832 as treatment for malignant cholera. He was building on work done by Dr. William O'Shaughnessy, which showed decreased amounts of water and salts in the blood of cholera patients, and after somewhat unsuccessful results with rectal delivery of salty solutions to cholera patients, Dr. Latta attempted direct intravenous replacement with impressive outcomes.[1,2] Intravenous saline administration remained controversial and fell out of favor until the late 1800s. In 1889, Dr. William Hunter delivered a series of 3 lectures on the physiology, pathology, and practice of transfusions, which were summarized in the British Medical Journal. In the last lecture, referring to the restoration of blood volume and blood pressure after hemorrhage, he stated "For practical purposes, however, all the advantages to be gained by transfusion may, I believe, be equally well and more readily obtained by infusion of a neutral saline, such as 3/4%."[3] By the early 1900s, intravenous fluid administration had gained acceptance in the medical community and been reported in the treatment of streptococcal sepsis, postpartum hemorrhage, and diabetic coma.[4]

Fast forward 100 years and intravenous hydration is now ubiquitous in medicine. It is so commonplace that fluids are often regarded as benign. Fluids are frequently given reflexively as first-line therapy in settings of hypotension, tachycardia, nausea, abdominal pain, acute kidney injury (AKI), electrolyte imbalances, and even during periods of fasting. Yet, recent data have shown the potential dangers associated with excessive or indiscriminate fluid administration, and the choice of fluid may have a significant impact on outcomes.

Therefore, fluid administration should be considered analogous to drug delivery. Just as when prescribing a drug, one must choose the correct compound and the correct dose and consider the possible side effects or consequences of an overdose. In this article, we review the current literature on the use of various resuscitation fluids in the intensive care unit (ICU) with particular attention to AKI and explore the dangers of fluid overload in critically ill patients.

FLUID CHOICES FOR RESUSCITATION

The physiologic goal of fluid resuscitation is to restore or maintain effective intravascular volume to assure adequate tissue perfusion. There are many different fluid preparations, and they should not all be regarded similarly. Fluids can be broadly categorized as either colloids or crystalloids.

Colloids are comprised of large molecular weight molecules, suspended within a solution, that generally do not diffuse across capillary membranes. As such, they have the theoretical advantage of staying in the vascular compartment and contributing to oncotic pressure, which in turn helps maintain intravascular volume. Colloids can be further subdivided into human albumin solutions vs synthetic colloids such as hydroxyethyl starches or gelatins. Crystalloids are solutions of ions that freely diffuse across the capillary membrane. Compared with colloids, crystalloids are far more widely available and significantly less expensive. However, because of diffusion outside the vascular space, larger volumes of crystalloids are needed compared with colloids, and there is increased risk for development of interstitial edema. Tables 1 and 2 provide a comparison of the various resuscitative fluids available in the United States.

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COLLOIDS

Albumin

In the early 1970s, use of human albumin solutions became increasingly prevalent in clinical practice, prompting a workshop at the National Institutes of Health in 1975 and the subsequent publishing of the first guidelines for clinical use of albumin.[5,6] These guidelines considered 4 clinical situations to be appropriate for albumin use: shock, burns, adult respiratory distress syndrome, and cardiopulmonary bypass.[6] Albumin use remained somewhat controversial, in part because of the significant expense, and several small clinical studies followed. In 1998, a Cochrane review concluded that the use of any type of albumin for the indications of hypovolemia, burns, or hypoproteinemia was associated with an increased risk of death as compared with crystalloids or no albumin at all.[7] However, the level of evidence remained poor overall.

The use of albumin as a resuscitation fluid was revisited in the Saline versus Albumin Fluid Evaluation (SAFE) randomized clinical trial in the early 2000s, which compared administration of 4% albumin to normal saline (NS) in 6997 adult patients admitted to an ICU with signs of volume depletion such as tachycardia, hypotension, poor capillary refill, low urine output, low central venous pressure, or low pulmonary capillary wedge pressure. At 28 days, there was no overall difference in mortality or need for renal replacement therapy (RRT).[8] However, a subgroup analysis of patients with severe sepsis suggested a mortality benefit when using 4% albumin compared with saline (adjusted mortality odds ratio 0.71, 95% confidence interval [CI] 0.52-0.97).[9] Conversely, another post-hoc analysis of this study found that albumin-based resuscitation was associated with higher mortality compared to saline in the subgroup of patients with traumatic brain injury.[10]

More recently, the Albumin Italian Outcome Sepsis study picked up where the SAFE study left off and investigated the use of albumin in patients with severe sepsis or septic shock. This open-label study enrolled 1818 patients from 100 different ICUs and randomized them to receive either crystalloids or crystalloids plus 20% albumin as fluid resuscitation.[11] Both groups were treated according to the principles of early goal–directed therapy (EGDT). The albumin group received an initial bolus of 300 mL 20% albumin and received continued albumin infusions as needed with a goal of maintaining serum albumin concentration greater than or equal to 30 g/L. Although the albumin group had improved hemodynamics and required fewer vasopressors, the primary outcome of death at 28 days was similar in both groups (relative risk [RR] 1.00, 95% CI 0.87-1.14). Secondary outcomes of death at 90 days (RR 0.94, 95% CI 0.85-1.05), degree of organ dysfunction, and length of ICU stay were also similar between the albumin and crystalloid groups.[11]

Based on the findings from the SAFE and Albumin Italian Outcome Sepsis trials, albumin and crystalloids appear to be equally effective fluids for general resuscitation or specifically for patients with severe sepsis. Considering the significantly greater cost associated with albumin, at present, there is insufficient evidence to support routine use of albumin in place of crystalloids.

CLINICAL SUMMARY

- There is no clear evidence to support colloids as first-line resuscitation fluids.
  - Randomized clinical trials, such as Saline versus Albumin Fluid Evaluation and Albumin Italian Outcome Sepsis, have found that resuscitation with albumin is associated with no difference in mortality or acute kidney injury (AKI) compared with crystalloids.
  - Starches, regardless of their molecular weight or substitution ratio, increase the risk of kidney injury when used as a resuscitation fluid.
- Crystalloids should remain the resuscitation fluid of choice.
  - Observational studies have suggested that use of chloride-rich crystalloid solutions are associated with worse outcomes (increased AKI or higher mortality) compared to balanced solutions.
  - The recently published randomized controlled 0.9% Saline vs Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy study found no difference in outcomes when comparing balanced vs chloride-rich solutions for resuscitation, but the predominantly surgical patient population required low volumes of fluid, and these results may not extend to intensive care unit patients who require larger volumes of resuscitative fluids.
- After initial resuscitation, positive fluid balances are associated with higher mortality.
  - Fluid overload, most commonly defined by either positive fluid balance or weight gain exceeding 10% of intensive care unit admission weight, has been variously associated with longer lengths of stay, higher mortalities, and decreased rates of recovery from AKI.

Starch

Synthetic hydroxyethyl starches (HESs) are available with varying molecular weights, percentage molecular substitution, and concentrations. Multiple randomized controlled studies have found that synthetic HES solutions increase the risk of kidney injury when used as a volume expander in the setting of severe sepsis. This effect seems to be greater with HES of higher molecular weight and higher degrees of molecular substitution.[12-15]

The most recent HES evaluation was the Crystalloid versus Hydroxyethyl Starch Trial.[15] This was a multicenter, prospective, randomized trial performed in New Zealand and Australia, in which 7000 adult ICU patients who required fluid resuscitation to maintain intravascular volume were randomized to receive either 6% HES (molecular weight 130 kDa, molar substitution ratio of 0.4) or 0.9% NS. Inclusion criteria were similar to those of the