Commentary

Albumin in critical care: SAFE, but worth its salt?

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Abstract

Intravascular fluid therapy is a common critical care intervention. However, the optimal type of resuscitation fluid, crystalloid or colloid, remains controversial. Despite the many theoretical benefits of human albumin administration in critically ill patients, there has been little evidence to support its widespread clinical use. Previous systematic reviews have led to conflicting results regarding the safety and efficacy of albumin. The recently reported Saline versus Albumin Evaluation study has provided conclusive evidence that 4% albumin is as safe as saline for resuscitation, although no overall benefit of albumin use was seen. Subgroup analysis of the albumin-treated group revealed a trend towards decreased mortality in patients with septic shock, and a trend towards increased mortality in trauma patients, especially those with traumatic brain injury. The results of these subgroups, as well as the use of higher albumin concentrations and other synthetic colloids (dextrans, starches), require rigorous evaluation in clinical trials. Finally, the Saline versus Albumin Evaluation trial represents a methodological milestone in critical care medicine, due to its size, its efficient trial design, and its logistical coordination. Future studies are still required, however, to establish a therapeutic niche for albumin and other colloids.

Keywords albumins, colloids, critical care, crystalloids, fluid therapy

Fluid resuscitation remains one of the most common therapeutic interventions performed on acutely ill patients in the intensive care unit. Despite this, the optimal type of fluid (crystalloid or colloid) employed, and its constituents, has been a source of controversy in the medical literature for many years. Human albumin administration has often been at the heart of this debate.

Albumin is one of the oldest known and studied human proteins. For example, Hippocrates was among the first to identify albumin in the foamy urine of people with chronic kidney disease [1]. Subsequent to its identification in both normal and pathologic conditions, purification and preparation of albumin in the laboratory became the focus of biochemists in the late nineteenth century and the early twentieth century. Medicinal uses for albumin did not arrive until World War II, however, where it was employed as a portable and easily stored blood plasma substitute ideal for the treatment of shock on the battlefield [1]. As a result of successful use during the war, albumin found its way into civilian hospitals and the volume expansion armamentarium of physicians, without the usual rigorous investigation now required of pharmaceuticals approved for use in humans.

Despite the fact that albumin has many theoretical advantages in critically ill patients, as a result of both its purported oncotic and nononcotic effects [2], there continues to be little quality evidence to support clinicians' utilization. In fact, many factors unrelated to evidence appear to be responsible for the clinician's choice of albumin [3]. There are limited data supporting the use of albumin in specific patient populations, including dialysis-related hypotension [4], following large volume paracentesis in diuretic refractory ascites [5], to prevent renal failure in spontaneous bacterial peritonitis associated with cirrhosis [6], and in acute respiratory distress syndrome [7]. However,

CI = confidence interval; SAFE = Saline versus Albumin Evaluation.

these limited data hardly justify the high-volume use of albumin in the intensive care unit.

As a result it has been difficult to rationalize continued use of albumin without further evidence. This is especially pertinent given the relatively high cost of albumin [8]. In 1998 clinicians felt increased pressure to justify their use of albumin when the Cochrane Injuries Group published a systematic review suggesting there may be a 6% (95% confidence interval [CI], 3–9%) absolute increase in mortality when albumin as compared with crystalloid solutions was used in critically ill patients with burns, hypovolemia, or hypoalbuminemia [9]. Perhaps it is no surprise that the use of albumin in the United Kingdom decreased by at least 40% following this publication [10]. Importantly, other subsequent systematic reviews [11–13] have led to conflicting results regarding albumin, and as such clinicians have been confused on the issue of the safety of albumin.

Finally, at least for critically ill patients, with the publication of the Saline versus Albumin Evaluation (SAFE) study, we have conclusive evidence that in the short-term albumin is at least as safe as saline for resuscitation [14]. This large, randomized clinical trial included a heterogeneous population of nearly 7000 critically ill patients requiring intravascular fluid resuscitation. The Australian and New Zealand Intensive Care Society Clinical Trials Group set out to determine the safety of fluid resuscitation with 0.9% normal saline versus 4% human albumin on a number of patient outcomes. There were no significant differences between the groups with respect to 28-day mortality, incidence of organ failure, intensive care unit or hospital length of stay, or duration of mechanical ventilation or renal replacement therapy. These results were achieved in the albumin arm with significantly less fluid administration, in a ratio of 1:1.4 (albumin versus normal saline) over the first 4 days. However, various subgroup analyses did reveal interesting results. There was a trend towards decreased mortality in septic shock patients treated with albumin (relative risk for death, 0.87; 95% CI, 0.74–1.02). Increased mortality in trauma patients (relative risk, 1.36; 95% CI, 0.99–1.86), especially those with traumatic brain injury (relative risk, 1.62; 95% CI, 1.12–2.34), was observed in the albumin treatment group.

There was no overall benefit associated with albumin use in the SAFE trial, although albumin use in septic shock patients may confer a survival advantage. Despite this interesting trend, it is worth noting that recent guidelines from the Surviving Sepsis Campaign and numerous professional critical care organizations advocate the equivalence of initial fluid resuscitation with either crystalloids or colloids (natural or artificial) in septic patients [15]. The biologic plausibility of improved outcome with albumin in sepsis has been examined in various *in vitro* and animal models, but the physiologic basis of this effect *in vivo* is not known [2]. The increased risk of mortality among trauma patients in the SAFE trial confirms a similar finding from a previous systematic review, where trauma patients who received crystalloids had a lower mortality rate than those who received colloids [13]. Interpretation of results from subgroup analyses requires caution and confirmation from properly designed clinical trials.

The results of the SAFE trial should ease clinician' fears about the short-term safety of albumin in critically ill patients. However, the safety of higher concentrations of albumin, such as 25%, remains unanswered. Moreover, several uncertainties exist regarding the use of synthetic colloids, such as dextrans and starches, in this population, as they have not undergone rigorous evaluation. Of note, preliminary data suggest that hydroxyethylstarch may be associated with poor outcomes when used in cardiopulmonary bypass (increased bleeding) [16] and in patients with sepsis (increased risk of renal failure) [17]. These fluids require equally rigorous evaluation. The results of the SAFE trial should also be a reminder to clinicians about the caution that needs to be used when applying the results of systematic reviews at the bedside (if, indeed, they are appropriate at all).

Finally, perhaps one of the greatest contributions of the SAFE trial has been the appreciation that, when several groups work together in a coordinated manner, this type of evaluation is achievable. This was the largest, multicenter, randomized trial in the critical care literature to date. It was performed with an Internet-based randomization scheme that was always accessible and applied by point-of-care staff. Through a partnership with industry (CSL Limited, Parkville, Victoria, Australia), specially designed fluid containers and administration sets were used to ensure effective double-blinding. The majority of study patients, nearly 95%, were enrolled using a provision for delayed consent. As a result, the SAFE trial was completed ahead of schedule. The investigators should be congratulated as, once again, the bar has been raised.

Despite the conclusions of the SAFE trial, clinicians are still left with the relatively high cost of albumin and little supporting data. Justification for continued use of albumin (and that of other colloids) needs to come from future trials focused on establishing and confirming its therapeutic niches.

Competing interests

The authors declare that they have no competing interests.

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